ANNALS
ACADEMY OF MEDICINE, SINGAPORE
COMMITTED TO SPECIALIST EDUCATION AND TRAINING SINCE 1957

VOLUME 50 | NUMBER 9 | FREE PAPERS | SEPTEMBER 2021 MCI (P) 020/06/2021

Early reperfusion of ST-segment elevation myocardial infarction (STEMI) leads to better outcomes. Interventions that have resulted in shorter door-to-balloon time include prehospital cardiovascular laboratory activation and prehospital electrocardiogram transmission, which are only available for patients who arrive via emergency ambulances.

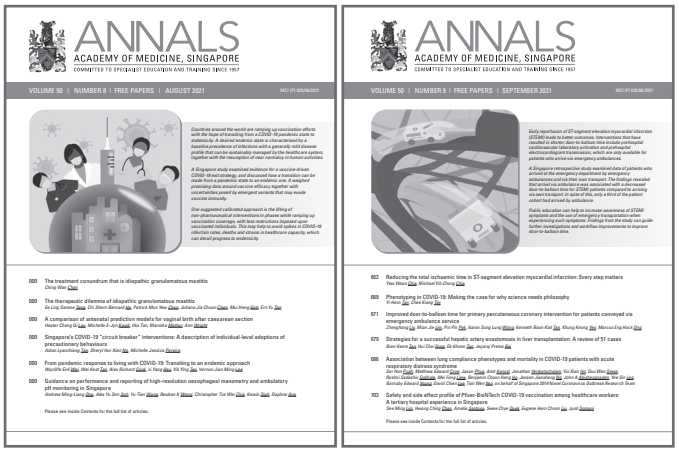
A Singapore retrospective study examined data of patients who arrived at the emergency department by emergency ambulances and via their own transport. The findings revealed that arrival via ambulance was associated with a decreased door-to-balloon time for STEMI patients compared to arriving via own transport. In spite of this, only a third of the patient cohort had arrived by ambulance.

Public education can help to increase awareness of STEMI symptoms and the use of emergency transportation when experiencing such symptoms. Findings from the study can guide further investigations and workflow to improve door-to-balloon time.

Please see inside Contents for the full list of articles.

ANNALS

Official Journal of the Academy of Medicine, Singapore



Call for Papers

The *Annals* is the official medical journal of the Academy of Medicine, Singapore. Established in 1972, the monthly peer-reviewed journal seeks to publish novel findings from clinical research and medical practices that can benefit the medical community.

The *Annals* is indexed in Index Medicus, Science Citation Index Expanded, ISI Alerting Services, and Current Contents/ Clinical Medicine. Impact Factor for the *Annals* in 2020 is 2.473 and 5-Year Impact Factor is 2.42.

The *Annals* welcomes manuscripts that advance the science and practice of medicine in these domains: ageing, chronic medical diseases and digital technology. A healthcare system that is more data-driven and patient-centric, leveraging on technology and digital solutions, will be areas warranting further research.

For guidance on manuscript preparation, instructions for authors are available at: https://www.annals.edu.sg/instructions.html. The descriptions and guidelines for all categories of articles that are published in the journal are available at: https://www.annals.edu.sg/pdf/Guidelines_for_Publication.pdf.

For submission of manuscript, please visit the online manuscript submission system: https://aams.manuscriptmanager.net. For queries on submission, please direct these to: annals@ams.edu.sg.

Annals, Academy of Medicine, Singapore
Volume 50 | Number 9 | September 2021

EDITORIALS

ORIGINAL ARTICLES

COMMENTARY

LETTERS TO THE EDITOR

IMAGES IN MEDICINE

EDITORIAL

Ann Acad Med Singap 2021;50:662-5
https://doi.org/10.47102/annals-acadmedsg.2021364

Reducing the total ischaemic time in ST-segment elevation myocardial infarction: Every step matters

Yew Woon Chia [1]*FRCP*, Michael Yih Chong Chia [2]*FRCEM*

Ischaemic heart disease (IHD) is the third leading cause of death in Singapore, accounting for 18.8% of all mortalities in 2019.[1] With our ageing population, there is an increased prevalence of cardiovascular risk factors such as hypertension, hyperlipidaemia and diabetes mellitus (15.6%, 13.6% and 6.9% of the population, respectively).[2] The Singapore Myocardial Infarction Registry (SMIR) revealed a significant increase in the crude incidence rate of acute myocardial infarction (AMI) from 235.6 to 364.8 per 100,000 population from 2010 to 2019, with a 30-day case fatality rate of 8.4%.[3]

In 1977, Reimer et al. elegantly described using experimental circumflex artery ligation the wavefront phenomenon of myocardial infarction propagation.[4] They demonstrated that myocardial necrosis started in the subendocardial myocardium after coronary artery occlusion and, with increasing duration of ischaemia, irreversible injury progressed as a wavefront towards the subepicardial myocardium. It was noted that after 40 minutes of occlusion, 55% of the myocardium at risk was still salvageable by reperfusion; by 3 hours, the salvageable area was down to 33%; and in 6 hours, only 16%. Therefore, any benefit of reperfusion therapy is time-dependent and should be implemented as soon as possible after an acute coronary artery occlusion to delay and prevent ischaemic myocardial cell death. Primary percutaneous coronary intervention (PCI) is now the preferred revascularisation strategy for ST-segment elevation myocardial infarction (STEMI) as it had demonstrated greater reduction in mortality, non-fatal reinfarction and stroke compared to thrombolytic therapy and is currently the standard of care for STEMI in Singapore.[5]

The "total ischaemic time" includes several key time intervals that are determinants of patient outcomes and should be systemically collected and analysed (Fig. 1). They include, temporally, time from symptom onset to first medical contact ("patient delay"), time from first medical contact to arrival at a PCI-capable centre ("emergency medical service [EMS] delay"), and time from arrival at a PCI-capable centre to revascularisation ("in-hospital delay" i.e. the "door-to-balloon" [DTB] time). The optimal approach to reduce each time interval differs in terms of strategy and medical resources needed.

With the recognition that earlier revascularisation confers better survival with less long-term adverse consequences e.g. poor left ventricular function, guidelines from international societies, such as the American College of Cardiology and American Heart Association, have advocated a DTB time of 90 minutes or less, which has become a key performance indicator in many healthcare systems.[6] DTB time refers to the time from arrival at the Emergency Department (ED) to restoration of antegrade flow down the infarct-related artery (either at the time of balloon inflation or wire crossing of the culprit lesion); it reflects the timeliness of hospitals in treating STEMI patients and quantifies the "in-hospital delay".

Is there a limit beyond which further reduction in the DTB time does not lead to additional improvement in clinical outcomes? Nallamothu et al. performed a multilevel model analysis of the US National Cardiovascular Data Registry (NCDR) CathPCI Registry and showed that every 10-minute reduction in patient-specific DTB time was strongly and consistently associated with lower in-hospital mortality (adjusted odds ratio [aOR] 0.92, 95% confidence interval [CI] 0.91–0.93, $P<0.0001$) and 6-month mortality (aOR 0.94, 95% CI 0.93–0.95, $P<0.0001$) at the individual patient-level although there was no association between decreases in annual DTB times and mortality at the population-level because of secular trends towards increased mortality risk in the primary PCI population.[7] More recently, a Taiwan registry demonstrated that patients with a DTB time of less than 60 minutes had lower incidences of thrombolysis in myocardial infarction flow grade less than 3 (aOR 0.4, 95% CI 0.20–0.76), 30-day reinfarction (aOR 0.3,

[1] Department of Cardiology, Tan Tock Seng Hospital, Singapore
[2] Department of Emergency Medicine, Tan Tock Seng Hospital, Singapore
Correspondence: A/Prof Yew Woon Chia, Department of Cardiology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: yew_woon_chia@ttsh.com.sg

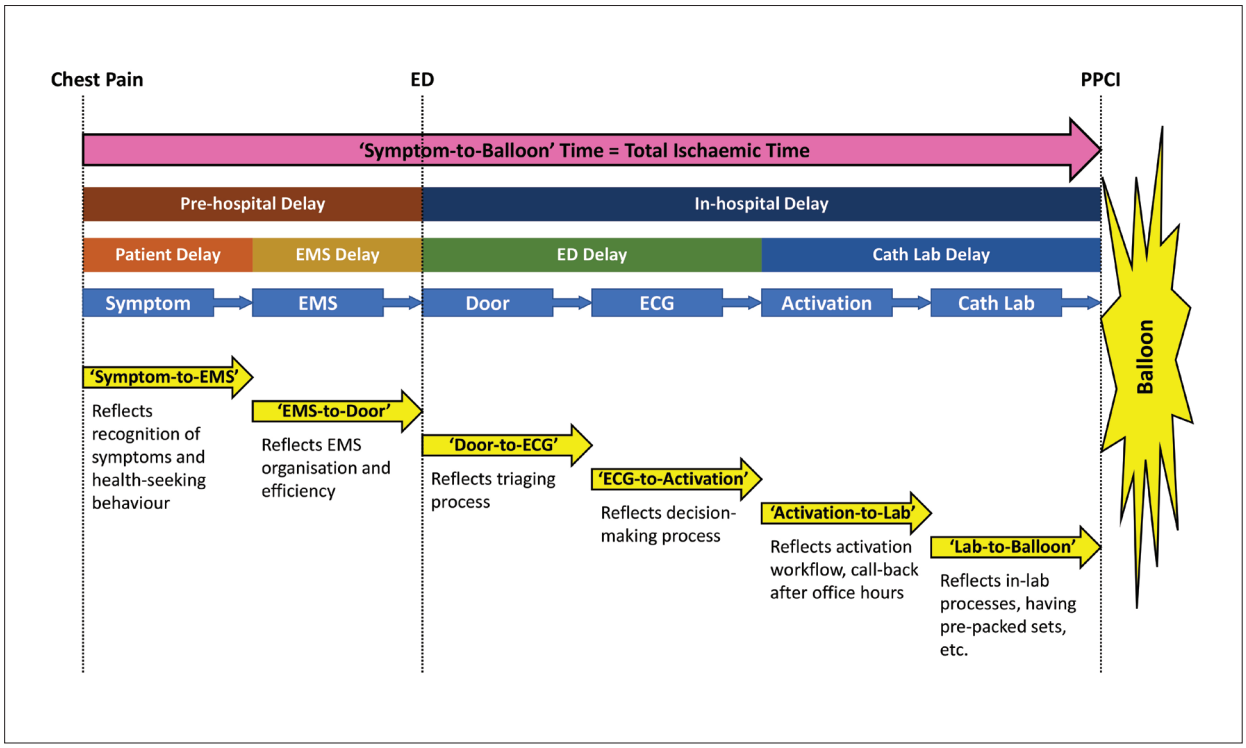


Fig. 1. The "Total Ischaemic Time", time intervals and components.
Cath Lab: cardiac catheterisation laboratory; ECG: electrocardiogram; ED: emergency department; EMS: emergency medical service; PPCI: primary percutaneous coronary intervention

95% CI 0.10–0.91) and 30-day mortality (aOR 0.3, 95% CI 0.09–0.77) than those with a DTB time of 60 to 90 minutes.[8] Park et al. also revealed, using the Korea Acute Myocardial Infarction Registry, that every 30-minute reduction in the DTB time showed continuous reduction in 1-year mortality (90 to 60 minutes: absolute risk reduction [ARR] 2.4%, number needed to treat [NNT] 41.9; 60 to 30 minutes: ARR 2.0%, NNT 49.2).[9]

The SMIR indicated that, barring exceptional cases of equivocal electrocardiographic (ECG) changes or patients who needed prolonged resuscitation or occasions when there were delays in obtaining informed consent, our local healthcare institutions are able to achieve a DTB time of 90 minutes or less in more than 90% of the time.[3] An earlier study by Sim et al. identified major system and non-system factors causing delays in the DTB time in a Singapore PCI-capable centre.[10] Among 1,268 STEMI patients who underwent primary PCI over a 4-year period, 202 (15.9%) had a DTB time of more than 90 minutes. The most common reasons were a delay in ED processes, atypical clinical presentation and unstable patient condition requiring stabilisation. It was reported that the delayed group had a 2.6% higher in-hospital mortality, although this did not reach statistical significance.

Initiatives to improve the DTB time have often focused on ED processes (e.g. "door-to-ECG" time, "door-to-cardiac catheterisation laboratory activation" time, "activation-to-arrival at cardiac catheterisation laboratory" time, etc.) and cardiac catheterisation laboratory processes (e.g. activation workflow especially after office hours, logistics such as having prepacked cardiac catheterisation sets, and having a well-rehearsed cardiac catheterisation team).[11] Improvements in these components have contributed to a significant reduction in the DTB time.

Optimal care of a STEMI patient demands a coordinated, multidisciplinary approach and prehospital processes play an equally significant role. In this issue of the *Annals*, Liu et al. performed a retrospective cohort study of 321 STEMI patients who presented to the ED of a PCI-capable centre and underwent primary PCI. They compared the DTB time between patients who arrived via emergency ambulances with those who self-conveyed to the hospital.[12] The investigators showed that the median DTB time was shorter for patients who were transported to the

hospital via the Singapore Civil Defence Force (SCDF) ambulances (52 minutes, interquartile range [IQR] 45–61) compared to those coming by their own transport (67 minutes, IQR 59–74, $P<0.001$). Furthermore, 74 (74.7%) patients in the ambulance group achieved a DTB time of less than 60 minutes compared to only 67 (30.2%) patients in the self-conveyance group. Nonetheless, the lack of a mortality benefit despite the shorter DTB time will need further evaluation. It might be because patients who came by the ambulances were sicker as shown in earlier studies.[13,14]

Liu et al. further analysed the components of the DTB time, which were affected by the different modes of transport, and revealed that the improvement in DTB time was attributed to a shortening in the ED processes, such as the door-to-ECG time and the door-to-activation time. This is not entirely surprising because when a STEMI diagnosis is suspected in the prehospital setting, the SCDF ambulance will convey the patient to a PCI-capable centre. The receiving hospital ED will also be notified to standby and the patient's ECG will be transmitted to the ED before ambulance arrival, which had been shown in a previous Singapore before-and-after study to reduce the DTB time by 23 minutes.[15] The awaiting ED team will also be primed to perform a confirmatory ECG immediately upon patient's arrival and the cardiac catheterisation team may also be activated in advance if the prehospital ECG is clearly diagnostic of a STEMI. Both prehospital ECG transmission and prehospital cardiac catheterisation laboratory activation, which are only possible when patients are conveyed by the emergency ambulances, can clearly contribute to a shorter DTB time.

It was noted that self-conveyed patients had a median door-to-ECG time (11 minutes, IQR 5–15 versus 1 minute, IQR 0–3; $P<0.001$) and a median door-to-activation time (18 minutes, IQR 12.0–25.0 vs 2 minutes, IQR 0.1–7.5; $P<0.001$), which were significantly longer compared to patients who arrived via the EMS. This provides an opportunity to explore quality improvement initiatives to reduce the gap and enhance the triaging of walk-in patients who may have symptoms suggestive of an AMI.[16] In addition, the authors revealed a significantly longer DTB time after office hours attributed to a 21.1% (95% CI 13.2–28.3, $P<0.001$) prolongation in the lab-to-balloon time. Healthcare institutions should collect more information on this and refine the activation workflow outside office hours.

While not specifically studied in the paper, conveyance by ambulance also provides an added layer of safety as AMI patients have a propensity to deteriorate and may go into cardiogenic shock or suffer a cardiac arrest en route to the ED. The patients are closely monitored in the ambulance and the trained paramedics will be able to commence immediate resuscitation, including providing supplementary oxygen, performing defibrillations and administering medications. All these may confer a higher chance of survival compared to patients taking either private or public transport to the hospital.

Unfortunately, only 99 (30.8%) patients in this study arrived in the ED via the EMS. Although the SMIR indicated an overall higher ambulance-conveyance rate of about 50%, this is still much lower compared to a Canadian registry of 59.9%.[14] There is certainly much work for the cardiovascular community to study the health-seeking behaviour of patients, educate the public in recognising the signs and symptoms of an AMI, and call 995 early.

Liu et al. had highlighted through the findings of their study the importance of public education to promote awareness of AMI symptoms and use of the EMS to improve STEMI outcomes. Concurrently, as there will always be self-conveyed patients, we should look at refining the triaging of patients who walk into ED with chest pain syndromes and how activation workflows can be enhanced after office hours.

The Singapore healthcare system has done well to meet the international benchmark DTB time of 90 minutes. We could certainly reduce this further but we should also look into shortening the prehospital delay (Fig. 1). We should collect routine data on "symptom-to-balloon" (STB) time as this reflects the total ischaemic time and had been shown to correlate better with infarct size and left ventricular ejection fraction compared to DTB time.[17] Importantly, the STB time incorporates a patient's dimension into the quality matrix as it includes the time from symptom onset to first medical contact (the "patient delay") and reflects the success of our public educational efforts. The trends of both DTB time and STB time should be monitored in a national STEMI registry with steps taken to identify and address system and non-system related delays.

Ultimately, the overarching goals in treating patients with AMI are to reduce their mortality and improve their left ventricular function. Beyond tracking time metrics such as DTB and STB times, the holistic management of a STEMI patient will also necessarily include compliance with guideline-directed medical therapy, aggressive cardiovascular risk factors control, lifestyle modifications, and participating in a tailored cardiac rehabilitation programme.

REFERENCES

1. Principal Causes of Death. Ministry of Health, Singapore. Available at: https://www.moh.gov.sg/resources-statistics/singapore-health-facts/principal-causes-of-death. Accessed on 6 September 2021.
2. National Population Health Survey Report 2019. Health Promotion Board, Singapore. Available at: https://www.hpb.gov.sg/community/national-population-health-survey/survey-findings. Accessed on 7 September 2021.
3. Singapore Myocardial Infarction Registry Annual Report 2019. National Registry of Diseases Office, Singapore. Available at: https://www.nrdo.gov.sg/publications/ami. Accessed on 6 September 2021.
4. Reimer KA, Lowe JE, Rasmussen MM, et al. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977;56:786-94.
5. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.
6. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol 2004;44:E1-211.
7. Nallamothu BK, Normand SL, Wang Y, et al. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. Lancet 2015;385:1114-22.
8. Chen FC, Lin YR, Kung CT, et al. The Association between Door-to-Balloon Time of Less Than 60 Minutes and Prognosis of Patients Developing ST Segment Elevation Myocardial Infarction and Undergoing Primary Percutaneous Coronary Intervention. Biomed Res Int 2017;2017:1910934.
9. Park J, Choi KH, Lee JM, et al. Prognostic Implications of Door-to-Balloon Time and Onset-to-Door Time on Mortality in Patients With ST-Segment-Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention. J Am Heart Assoc 2019;8:e012188.
10. Sim WJ, Ang AS, Tan MC, et al. Causes of delay in door-to-balloon time in south-east Asian patients undergoing primary percutaneous coronary intervention. PLoS One 2017;12:e0185186.
11. Krumholz HM, Bradley EH, Nallamothu BK, et al. A campaign to improve the timeliness of primary percutaneous coronary intervention: Door-to-Balloon: An Alliance for Quality. JACC Cardiovasc Interv 2008;1:97-104.
12. Liu Z, Lim MJ, Pek PP, et al. Improved door-to-balloon time for primary percutaneous coronary intervention via emergency ambulance service. Ann Acad Med Singap 2021;50:671-8.
13. Chia YC. Modes of arrival, door to balloon time and its impact on morbidity and mortality for ST elevation myocardial infarct. Crit Care 2012;16(Supp 1):P183.
14. So DY, Ha AC, Turek MA, et al. Comparison of mortality patterns in patients with ST-elevation myocardial infarction arriving by emergency medical services versus self-transport (from the prospective Ottawa Hospital STEMI Registry). Am J Cardiol 2006;97:458-61.
15. Ong ME, Wong AS, Seet CM, et al. Nationwide improvement of door-to-balloon times in patients with acute ST-segment elevation myocardial infarction requiring primary percutaneous coronary intervention with out-of-hospital 12-lead ECG recording and transmission. Ann Emerg Med 2013;61:339-47.
16. Lee CK, Meng SW, Lee MH, et al. The impact of door-to-electrocardiogram time on door-to-balloon time after achieving the guideline-recommended target rate. PLoS One 2019;14:e0222019.
17. Redfors B, Mohebi R, Giustino G, et al. Time Delay, Infarct Size, and Microvascular Obstruction After Primary Percutaneous Coronary Intervention for ST-Segment-Elevation Myocardial Infarction. Circ Cardiovasc Interv 2021;14:e009879.

EDITORIAL

Ann Acad Med Singap 2021;50:666-8
https://doi.org/10.47102/annals-acadmedsg.2021332

Hepatic artery anastomosis in liver transplantation

Siew-Weng Ng [1] *FRCS (Edin)*

Liver transplant is the definitive therapy for end-stage liver failure. The challenges include overcoming technical difficulties of the transplant surgery followed by medical therapy to prevent organ rejection. The most important surgical hurdle is the prevention of hepatic artery thrombosis (HAT) that can occur in up to 9% of cases.[1,2]

The native liver is able to tolerate significant ischaemia with rich collateral supply but the biliary system is primarily supplied by the hepatic artery. HAT in the transplanted liver is poorly tolerated with graft loss and more than 50% mortality and a 75% incidence of retransplantation.[3] Jain et al. noted that in 4,000 consecutive liver transplants at the University of Pittsburgh, one third of retransplantations was caused by HAT and technical failure was the main reason.[4] Early detection and prevention of HAT is most dependent on microvascular surgical techniques and the regular use of Doppler ultrasound screening.[5]

In Singapore, at least 30% of liver transplant involves living donors due to a low donation rate.[6] Compared with deceased donor liver transplantation (DDLT), living donor liver transplantation (LDLT) is associated with higher incidences of hepatic artery thrombosis, thus increasing the risk of morbidity and mortality. The donor vessels in LDLT are usually smaller and shorter, thereby increasing technical difficulty.[7] To address this, a collaborative effort between the transplant surgeon and plastic surgery team at the Singapore General Hospital was established. There was a lower incidence of short- and long-term arterial complications, especially in LDLT when the plastic surgery team performed arterial anastomosis under microscopy.[6]

In this issue of the *Annals*, Tan et al. reviewed 51 consecutive cases of liver transplantation (31 cases of DDLT and 20 cases of LDLT) at the Singapore General Hospital from January 2015 to December 2018.[8] The mean age was 58 and the most common indications for liver transplantation were non-alcoholic steatohepatitis, alcoholic liver disease and chronic hepatitis. A transplant surgeon performed the initial anastomoses of hepatic and portal veins. This was followed by arterial anastomoses under microscopy (10x magnification) by a pair of plastic surgeons. The transplant team then completed the transplant with biliary reconstruction. Serial postoperative ultrasound examinations were done on day 1, 3, 5, 7, 9 and 14 to assess patency of the hepatic artery and biliary reconstruction.

A total of 61 arterial anastomoses were performed. There was 1 incident of hepatic thrombosis that was salvaged successfully with a radial artery interpositional graft. The hepatic arterial anastomosis was fraught with difficulties: small and short donor vessels (especially in LDLT); poor vessel quality; mismatch between donor and recipient vessel size; and microsurgery in deep recess worsened by respiratory movements. The authors outlined the technical challenges faced and illustrated the various techniques used to improve outcome for the important step of arterial reconstruction in liver transplantation.

In general, the planning of arterial anastomosis need careful consideration of (1) choice of recipient vessels; (2) methods to overcome vessel length deficiency; (3) careful preparation of poor quality vessels; and (4) meticulous techniques for anastomosis.

Choice of recipient vessels. The recipient vessel of choice is the right or left hepatic artery. However, where there is a donor vessel size mismatch, the site of recipient arterial anastomosis would need to be more proximal. This site ranges from the hepatic artery proper or the take-off of the splenic artery all the way up to the common hepatic artery. The arterial anastomosis may also be sited upstream if there is possible damage to the hepatic artery after transarterial chemoembolisation (TACE), in which case the gastroduodenal artery can be used instead.

Another situation for proximal anastomosis is when 2 recipient vessels are needed to vascularise a large liver graft. This duo anastomosis configuration may involve the gastroduodenal and common hepatic arteries. In an extreme situation of HAT salvage, revascularisation using the right gastroepiploic artery has been described.[9]

[1] Sweng Plastic Aesthetic and Reconstructive Surgery, Farrer Park Hospital, Singapore
Correspondence: Dr Siew-Weng Ng, Sweng Plastic Aesthetic and Reconstructive Surgery, Farrer Park Hospital, 1 Farrer Park Station Road, #16-08 to 10 Connexion, Singapore 217562.
Email: sweng8@gmail.com

Options for short vessels. Vessel length deficiency may be encountered in LDLT or in HAT salvage after thrombectomy and trimming of vessels. An arterial or venous interpositional vessel graft may serve as a vascular funnel where vascular inflow and outflow mismatch.

Venous grafts (e.g. from the saphenous or common iliac vein) tend to be thinner and dilate post-manipulation. A thrombosis rate of up to 23.8% has been reported,[10] with long-term patency rate of less than 50% at 10 years.[11] However, vein grafts have also been reportedly used with good effects in head and neck arterial reconstruction,[12] as well as severe vasospastic condition.[13] Arterial grafts are generally preferred for better patency rates—up to 83% at 5 years in coronary bypass has been reported.[14,15] The radial artery interpositional graft is a common choice. The descending branch of lateral circumflex femoral artery can be used for patients with an abnormal Allen's test result.[16] This option provides a long length and possible Y-shape configuration for double anastomoses.

The need to use interpositional graft, which increases the number of anastomoses, needs to be weighed against the increased risk of early HAT.[17] This risk is increased by twofold for every extra anastomosis.

Preparation of poor quality vessels. The hepatic vessels tend to be of poor quality in liver transplantation. They can be fibrotic from previous peritonitis, or atherosclerotic related to a fatty liver, or fragile after TACE. Tan et al. outlined the steps taken to prepare the vessels for anastomosis in a deep recess using customised instruments. The vessels were trimmed using a number 11 blade held by a specially angled blade holder, on a custom-bent angulated platform for support. It was important not to skeletonise the adventitia.

Anastomotic techniques. Several important pointers were discussed by the authors to overcome the problem of friable vessels with a tendency to tear or delaminate. The anastomosis was done with 8/0 suture at varying distances from the vessel edge. The staggered suturing pattern decreased the risk of circumferential tear of friable vessels. If there was a tendency for endothelial delamination, the stitching was done inside-out with the needle tagging against the endothelium downwards, rather than lifting off if the needle entered from outside-in. If both recipient and donor vessels had a tendency to delaminate, every stitch was done in the inside-out manner, thus using a single strand of dual-ended suture for each stitch of the anastomosis. The adventia was then closed with 9/0 suture to improve the seal. Fibrin glue was then sprayed over and around the anastomosis, akin to having a sealant to set the vessels in the desired orientation to optimise the lie and prevent any kinking.

The discussed methodologies are essential for good vessel coaptation. The anastomosis should be watertight with no intimal damage or exposure, tension-free with no length redundancy, laid in a manner to avoid kinking or compression of vessels (by the biliary system).

Further development. With the advent of supermicrosurgical techniques for vessels less than 1mm in diameter, it may be feasible to anastomose very small donor vessels to the recipient hepatic arterial system in an end-to-side manner.[18] This may require special double-ended short strands of fine sutures, possibly using intraoperative indocyanine green angiography to verify patency.

Further improvement in liver transplantation outcome may be possible with the use of implantable Doppler to continuously monitor the status of the anastomosis. Implantable Doppler improved the lead time for identifying vascular compromise by an average of 10 hours, providing a specificity of 94.44% and positive predictive value of 66.66% with an overall accuracy of 95%.[19] In another study, the sensitivity and specificity of implantable Doppler has been reported to be as high as 100%.[20] Any abnormal findings by an implantable Doppler would still require confirmation by conventional transcutaneous Doppler.

In conclusion, hepatic artery reconstitution is one of the most important and challenging steps of liver transplantation. In comparison with most free flap reconstruction surgery, the liver transplantation patient is usually in a poorer nutritional state, with a suboptimal coagulation profile. The liver graft is probably a more precious resource than the autologous musculocutaneous free flap harvested from the patient. The recipient vessel quality may be worse than those encountered in crush injury and less amenable to further cutback. There is the additional technical challenge of performing anastomosis in a deep recess, interrupted by respiratory movement. Therefore, it is exemplary to engage a team of experienced microsurgeons to organise the harvest of interpositional graft if needed, and perform the critical anastomosis to ensure the best outcome—what is often described as one-bite-of-the-cherry. These coordinated efforts are well illustrated in the article by Tan et al. with a very successful outcome.

REFERENCES

1. Proposito D, Loinaz Segurola C, Garcia Garcìa I, et al. Assessment of risk factors in the incidence of hepatic artery thrombosis in a consecutive series of 687 liver transplantations. Ann Ital Chir 2001;72:187-205.
2. Abou Ella KA, Al Sebayel MI, Ramirez CB, et al. Hepatic artery thrombosis after orthotopic liver transplantation. Saudi Med J 2001;22:211-4.
3. Stange BJ, Glanemann M, Nuessler NC, et al. Hepatic artery thrombosis after adult liver transplantation. Liver Transpl 2003; 9:612-20.
4. Jain A, Reyes J, Kashyap R, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. Ann Surg 2000;232:490-500.
5. Heaton ND. Hepatic artery thrombosis: conservative management or retransplantation? Liver Transpl 2013;19:S14-S6.
6. Tan EK, Tan BK, Fong HC, et al. Impact of microsurgical anastomosis of hepatic artery on arterial complications and survival outcomes after liver transplantation. Transplant Proc 2021; 53:65-72.
7. Okochi M, Ueda K, Hirose T, et al. A modified technique for hepatic artery reconstruction in living donor liver transplantation. Microsurgery 2010;30:541-4.
8. Tan BK, Fong HC, Tan EK, Raj JP. Strategies for a successful hepatic artery anastomosis in liver transplantation: A review of 51 cases. Ann Acad Med Singap 2021;50:679-85.
9. Ikegami T, Kawasaki S, Hashikura Y, et al. An alternative method of arterial reconstruction after hepatic arterial thrombosis following living related liver transplantation. Transplantation 2000;69:1953-5.
10. Tzakis AG, Gordon RD, Shaw BW Jr, et al. Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporin era. Transplantation 1985;40:667-71.
11. Campeau L, Enjalbert M, Lesperance J, et al. Atherosclerosis and late closure of aortocoronary saphenous vein graft: sequential angiographic studies at 2 weeks, 1 year, 5 to 7 years, and 10 to 12 years after surgery. Circulation 1983;68:II1-117.
12. Koshima I, Yamamoto H, Hosoda M, et al. Free combined composite flaps using the lateral circumflex femoral system for repair of massive defects of the head and neck regions: an introduction to the chimeric flap principle. Plast Reconstr Surg 1993;92:411-20.
13. Kim YH, Ng SW, Seo HS, et al. Classification of Raynaud's disease based on angiographic features. J Plast Reconstr Aesthet Sur 2011;64:1503-11.
14. Acar C, Jebara VA, Portoghese M, et al. Revival of the radial artery for coronary artery bypass grafting. Ann Thorac Surg 1992; 54:652-60.
15. Dietl CA, Benoit CH. Radial artery graft for coronary revascularization: technical considerations. Ann Thorac Surg 1995;60:102-110.
16. Imakuma ES, Bordini AL, Millan LS, et al. Comparative morphometric analysis of 5 interpositional arterial autograft options for adult living donor liver transplantation. Transplant Proc 2014;46:1784-8.
17. Piscaglia F, Vivarelli M, La Barba G, et al. Analysis of risk factors for early hepatic artery thrombosis after liver transplantation. Possible contribution of reperfusion in the early morning. Dig Liver Dis 2007;39:52-9.
18. Iida T, Yoshimatsu H, Yamamoto T, et al. A pilot study demonstrating the feasibility of supermicrosurgical end-to-side anastomosis onto large recipient vessels in head and neck reconstruction. J Plast Reconstr Aesthet Surg 2016;69:1662-8.
19. Vasant Kulkarni S, Rao PP, Naidu CS, et al. Evaluation of implantable Doppler probe continuous monitoring of hepatic artery anastomosis after liver transplantation. Med J Armed Forces India. 2021;77:349-54.
20. Guillemaud JP, Seikaly H, Cote D, et al. The implantable Cook-Swartz Doppler probe for postoperative monitoring in head and neck free flap reconstruction. Arch Otolaryngol Head Neck Surg 2008;134:729-34.

EDITORIAL

Ann Acad Med Singap 2021;50:669-70
https://doi.org/10.47102/annals-acadmedsg.2021310

Phenotyping in COVID-19: Making the case for why science needs philosophy

Yi-Hern Tan [1]*MRCP (Edin)*, Chee Kiang Tay [1]*MRCP (Lond)*

COVID-19 pneumonia is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Among patients with SARS-CoV-2 infection, the most frequent reason for intensive care unit (ICU) admission is the development of acute respiratory distress syndrome (ARDS) and consequent hypoxaemia.[1]

There has been much academic discourse and debate around clinical phenotypes of COVID-19-associated ARDS (CARDS). Gattinoni et al. first described the unusual combination of profound hypoxaemia and relatively preserved lung compliance in a series of COVID-19 patients with ARDS.[2] Based on distinct physiologic profiles observed in their case series, they postulated that 2 distinct phenotypes exist: type L that is primarily characterised by low elastance and low recruitability, and type H that is more akin to typical severe ARDS with high elastance and high recruitability. By attributing hypothesised differences in lung mechanics and pathophysiologic mechanisms to type L CARDS, they posited tailored treatments that ran counter to evidence-based recommendations in the management of ARDS.[3] It is our view that this postulation, which became a trending topic in no time, did engender a welcomed shift in CARDS treatment from the frenetic chase for effective therapeutics to pathophysiology-based intensive care management. At this juncture, it is pertinent to highlight that the concept of phenotyping ARDS is neither a novel nor recent phenomenon. Investigators had previously identified hyperinflammatory and hypoinflammatory subphenotypes in non-COVID-19 ARDS, and the implications of this dichotomy on treatment.[4,5]

In this issue of the *Annals*, Puah et al. described a prospective cohort study that examined factors associated with mortality in 102 mechanically ventilated patients with CARDS.[6] Older age, use of high-flow nasal cannula (HFNC), and acute kidney injury (AKI) and/or renal replacement therapy correlated with higher mortality. Post-intubation static compliance (C_{stat}) data were available for 67 patients. Using a C_{stat} threshold of 40mL/cm H_2O, 24 (35.8%) and 43 (64.2%) patients were classified as high and low compliance phenotypes, respectively.[7] Follow-up C_{stat} data at 1-week post-intubation were available for 29 patients (12 and 17 patients in the high and low compliance groups, respectively). A significant reduction in C_{stat} (-10.5 mL/cm H_2O, interquartile range -4.9 to -18.15; P=0.01) was observed only in the high compliance group. Patients in this group also had higher mortality (33.3% versus 11.6%; P=0.03); this observation remained statistically significant after correcting for age, use of HFNC and AKI (odds ratio 3.5, 95% confidence interval 1.1–12; P=0.04). The authors likened the high compliance phenotype in their study to previously described ARDS subtypes such as the hypoinflammatory phenotype 1 by Calfee et al.[4] and focal ARDS by Constantin et al.[8] However, no significant between-group differences in inflammatory biomarkers, e.g. C-reactive protein or procalcitonin were found to support this hypothesis.

The study findings suggest that CARDS patients who presented with higher C_{stat} that subsequently deteriorated are at a higher risk of death. However, it is imperative to evaluate the limitations and context of this study before the findings could be interpreted plainly. First, only 67 patients had post-intubation C_{stat} measurements, with less than half of them having a repeat measurement on day 7 after intubation. Considering that the median duration of mechanical ventilation was 11–12 days in this subgroup, it remains unclear if the marked "attrition" in numbers could be mostly accounted for by patients who had recovered quickly and adequately to undergo weaning or liberation from mechanical ventilation. Second, data such as the onset of symptoms and hypoxaemia/respiratory failure preceding intubation were unreported. As heterogeneity in CARDS (e.g. clinical trajectory, pathophysiologic mechanisms, respiratory mechanics and inflammatory profiles) is increasingly recognised, inclusion of time-related variables could reduce their potential confounding effects on study results.[9] Third, this study was conducted relatively early during the COVID-19 pandemic in Singapore. Following this study, dexamethasone and remdesivir were shown to have potentially important clinical benefits in mechanically ventilated patients with severe COVID-19 pneumonia, and are now

[1] Department of Respiratory & Critical Care Medicine, Singapore General Hospital, Singapore
Correspondence: Dr Chee Kiang Tay, Department of Respiratory & Critical Care Medicine, Singapore General Hospital, 20 College Road, Academia, Level 3, Singapore 169856.
Email: melvin.tay.c.k@singhealth.com.sg

recommended as standard-of-care for this patient subgroup.[10-12] Notwithstanding the unknown impact of these therapeutics on pulmonary physiology and mechanical ventilation, the effect is largely mitigated by the study's impressively low mortality rate of 14.7%. Finally, analysis using data from the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE) study—a multinational ESICM-led prospective cohort study—revealed a wide range of respiratory system compliance (C_{rs}) among 1,171 non-COVID ARDS patients with 1 in 8 having preserved compliance, and that lower C_{rs} was independently associated with higher mortality.[13] In other words, the so-called type L CARDS phenotype existed even before the current pandemic among patients with ARDS. Rather than a novel disparate entity, it is more appropriate to conclude that it lies on a spectrum of the same clinical syndrome, namely ARDS.

The take-home message from the evolving narrative of COVID-19 phenotyping is perhaps best encapsulated by the words, "purpose", "process" and "pragmatism". Phenotyping should have a clear purpose that is preferably actionable, e.g. an intervention that leads to improved patient-centred outcome.[14] It is equally important to recognise that scientific rigour is requisite in the phenotyping process that entails among others: systematic data collection from large multicentre cohorts, robust and unbiased statistical data analysis, internal consistency measurements, and demonstration of reproducibility via prospective validation in disparate cohorts.[14,15] Lastly, it is easy to be overwhelmed by an overload of new information (whether true or false) in this digital age. In philosophy, one of the core tenets in pragmatism is enquiry, which as pragmatists are persuaded, requires a presuppositionless starting-point that is only possible in the presence of doubt. Perhaps more so than ever, science needs philosophy.[16]

REFERENCES

1. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med 2020;8:506-17.
2. Gattinoni L, Coppola S, Cressoni M, et al. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2020;201:1299-300.
3. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46:1099-102.
4. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2014; 2:611-20.
5. Famous KR, Delucchi K, Ware LB, et al. Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy. Am J Respir Crit Care Med 2017; 195:331-8.
6. Puah SH, Cove ME, Phua J, et al. Association between lung compliance phenotypes and mortality in COVID-19 patients with acute respiratory distress syndrome. Ann Acad Med Singap 2021; 50:686-94.
7. Bos LDJ, Paulus F, Vlaar APJ, et al. Subphenotyping Acute Respiratory Distress Syndrome in Patients with COVID-19: Consequences for Ventilator Management. Ann Am Thorac Soc 2020;17:1161-3.
8. Constantin JM, Jabaudon M, Lefrant JY, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. Lancet Respir Med 2019;7:870-80.
9. Fan E, Beitler JR, Brochard L, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? Lancet Respir Med 2020;8:816-21.
10. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021;384:693-704.
11. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020; 383:1813-26.
12. National Institutes of Health. COVID-19 Treatment Guidelines: What's new in the Guidelines, 2021. Available at: https://www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new. Accessed on 11 August 2021.
13. Panwar R, Madotto F, Laffey JG, et al. Compliance Phenotypes in Early Acute Respiratory Distress Syndrome before the COVID-19 Pandemic. Am J Respir Crit Care Med 2020;202:1244-52.
14. Bos LDJ, Sinha P, Dickson RP. The perils of premature phenotyping in COVID-19: a call for caution. Eur Respir J 2020;56:2001768.
15. National Institutes of Health. Rigor and Reproducibility. Available at: https://www.nih.gov/research-training/rigor-reproducibility. Accessed on 11 August 2021.
16. Laplane L, Mantovani P, Adolphs R, et al. Opinion: Why science needs philosophy. Proc Natl Acad Sci USA 2019;116:3948-52.

ORIGINAL ARTICLE

Ann Acad Med Singap 2021;50:671-8
https://doi.org/10.47102/annals-acadmedsg.2021153

Improved door-to-balloon time for primary percutaneous coronary intervention for patients conveyed via emergency ambulance service

Zhenghong Liu [1]*MBBS*, Mian Jie Lim [2]*MBBS*, Pin Pin Pek [1,3]*MPH*, Aaron Sung Lung Wong [4]*MRCP(UK)*, Kenneth Boon Kiat Tan [1]*MMed (EM)*, Khung Keong Yeo [4]*ABIM*, Marcus Eng Hock Ong [1,4]*MPH*

ABSTRACT

Introduction: Early reperfusion of ST-segment elevation myocardial infarction (STEMI) results in better outcomes. Interventions that have resulted in shorter door-to-balloon (DTB) time include prehospital cardiovascular laboratory activation and prehospital electrocardiogram (ECG) transmission, which are only available for patients who arrive via emergency ambulances. We assessed the impact of mode of transport on DTB time in a single tertiary institution and evaluated the factors that affected various components of DTB time.

Methods: We conducted a retrospective cohort study using registry data of patients diagnosed with STEMI in the emergency department (ED) who underwent primary percutaneous coronary intervention. We compared patients who arrived by emergency ambulances with those who came via their own transport. The primary study end point was DTB, defined as the earliest time a patient arrived in the ED to balloon inflation. As deidentified data was used, ethics review was waived.

Results: A total of 321 patients were included for analysis after excluding 7 with missing data. The mean age was 61.4±11.4 years old with 49 (15.3%) females. Ninety-nine (30.8%) patients arrived by emergency ambulance. The median DTB time was shorter for patients arriving by ambulance versus own transport (52min, interquartile range [IQR] 45–61 vs 67min, IQR 59–74; $P<0.001$), with shorter door-to-ECG and door-to-activation time.

Conclusion: Arrival via emergency ambulance was associated with a decreased DTB for STEMI patients compared to arriving via own transport. There is a need for public education to increase the usage of emergency ambulances for suspected heart attacks to improve outcomes.

Ann Acad Med Singap 2021;50:671-8

Keywords: Cardiovascular lab activation, door-to-balloon time, emergency ambulance, primary PCI, STEMI

INTRODUCTION

Early reperfusion of ST-segment elevation myocardial infarction (STEMI) has been shown to result in better outcomes,[1-3] and guidelines for treatment of STEMI recommend a rapid and coordinated response.[4] The American Heart Association guidelines released in 2014 recommend a door-to-balloon (DTB) time of less than 90 minutes,[5] and timings of less than 60 minutes have been associated with better outcomes.[6]

In Singapore, patients presenting to the emergency departments (ED) of our public hospitals with acute STEMI are usually offered emergency percutaneous coronary intervention (PCI) as first-line treatment. In line with international recommendations, the national target for DTB time is 90 minutes. This target is met by public hospitals more than 90% of the time.[7]

Worldwide, interventions that have resulted in shorter DTB time include direct emergency physician activation of cardiovascular laboratory (CVL), prehospital CVL activation and prehospital electrocardiogram (ECG) transmission.[8-10]As these interventions are only available to patients being conveyed by emergency ambulances, it is recommended that patients should call an emergency ambulance when experiencing symptoms such as severe

[1] Department of Emergency Medicine, Singapore General Hospital, Singapore
[2] SingHealth Emergency Medicine Residency Programme, SingHealth, Singapore
[3] Prehospital and Emergency Research Centre, Health Services and Systems Research, Duke-NUS Medical School, Singapore
[4] Department of Cardiology, National Heart Centre Singapore, Singapore
Correspondence: Dr Zhenghong Liu, Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608.
Email: liu.zhenghong@singhealth.com.sg

CLINICAL IMPACT

What is New

- This study shows that emergency ambulance usage is associated with shorter door-to-balloon (DTB) time largely due to shorter door-to-electrocardiogram timing.
- Other aspects that require attention include after-office-hours timing.

Clinical Implications

- The study supports the need to increase the awareness and usage of emergency ambulances when a heart attack is suspected.
- The findings can guide further investigations and quality improvement projects to reduce DTB time.

chest pain, especially when associated with sweating, breathlessness, nausea or vomiting. Despite this, some international studies report that only 60% of STEMI patients use an ambulance.[11] In Singapore, a previous study found that only 50% percent of STEMI patients come to hospital by emergency ambulance.[12]

We aimed to study the impact of mode of arrival on DTB time in our institution, Singapore General Hospital. We hypothesise that usage of emergency ambulances will be associated with shorter DTB time compared to arriving via own transport. Subsequently, we aimed to analyse the impact of mode of transport on the various components of DTB time. Amongst patients conveyed by emergency ambulances, we further analysed the impact of hospital ED standby, ECG transmission and CVL activation on the various components of DTB time.

METHODS

Study design

We conducted a single-centre retrospective cohort study of all patients who underwent emergency PCI for STEMI from the ED from January 2018 to August 2019. We conducted a chart review combining emergency department records, cardiology department registry data, as well as an ongoing national myocardial infarction registry. Ethics review was waived by the SingHealth Centralised Institutional Review Board (2020/3011).

Setting

Singapore General Hospital is Singapore's largest tertiary hospital with 1,735 beds. The ED sees an annual volume of more than 125,000 patients, with emergency PCI supported by the National Heart Centre Singapore, a specialist heart centre.

All patients presenting to the ED with a complaint that could represent an acute coronary syndrome are prioritised for an ECG. This is done in the ambulatory triage area for ambulatory patients and in the critical care area for non-ambulatory patients. All ECGs are immediately reviewed by a senior doctor, who would assess for the presence of STEMI.

Singapore's emergency medical services system is run by the Singapore Civil Defence Force (SCDF). The service is activated by a centralised 995 dispatching system, with the service handling 191,468 ambulance calls in 2019.[13] SCDF's 60 ambulances are manned by specially trained paramedics, who are able to put an ED on standby for patients in whom they suspect a STEMI, and are also able to fax ECGs on route to the ED. On receipt of an ECG diagnostic of a STEMI, the emergency physician has the option to activate the CVL lab prior to the patient's arrival.[9,12]

Data source and study population

All patients who presented to the ED with STEMI and subsequently underwent emergency PCI were included for analysis. Patients with missing data on mode of arrival or DTB time were excluded from analysis.

We obtained the list of patients from the Primary PCI database that is maintained by the National Heart Centre Singapore. This database comprises patients who underwent primary PCI from the emergency department. It contains demographic data and a breakdown of the components of DTB time, including the time of arrival, time of ECG, time of CVL activation, time of arrival to the CVL lab, as well as time of perfusion. The database has exclusion criteria that exclude patients who suffered a cardiac arrest, had cardiogenic shock requiring resuscitation or showed a non-diagnostic ECG. As such, only patients with clear STEMI on ECG and did not require prolonged resuscitation in the ED were included in this cohort. Full exclusion criteria are available in Table S1 of Supplementary Materials (in the online version of this article.)

Data on mode of arrival were obtained from the ED records. The triage note written by nurses contains information on the mode of arrival. We also matched outcomes from the Singapore Myocardial Infarction Registry,[14] which is a national registry that contains outcome data pertaining to our patients. We also accessed the SCDF ECG transmission records to identify patients for whom prehospital ECGs were transmitted. Data were extracted by 2 study team members, with disagreements resolved by consensus.

Study variables

Our primary outcome was DTB time in minutes, defined as the earliest time the patient was registered in the ED to the time the balloon was inflated. We also examined inpatient mortality as well as the components of DTB time as secondary outcomes, such as door-to-ECG time, and door-to-CVL time. Components of DTB time were recorded by the ED staff and CVL staff, and extracted from the Primary PCI database.

The independent variable was mode of arrival, which was obtained from the ED patient records. Other independent variables included prehospital transmission of ECG as well as whether the ED was put on standby. These were obtained from the ED records and SCDF ECG transmission records.

Data analysis

We described patient characteristics using percentages for categorical data. Mean and standard deviation, or median and interquartile range (IQR) were used for normally and non-normally distributed continuous variables, respectively. Statistical comparisons for differences in baseline characteristics among patients arriving by emergency ambulance and own transport were performed using chi-square tests for categorical variables. T-test and Wilcoxon rank-sum test were used for normally and non-normally distributed data, respectively. DTB time and its components were described using median and IQR based on mode of transport.

Subsequently, we conducted multivariable linear regression with DTB time in minutes as the primary outcome. For the predictors, we included factors that have been reported to be associated with DTB time, including age, sex, presentation during working hours, and ambulance usage.[15,16] Secondary outcomes include door-to-ECG time, door-to-activation time, activation-to-lab time and lab-to-balloon time.

The primary and secondary endpoints (in minutes) were log transformed for use in regression models to maintain normality. Statistical output is therefore reported as percent change in time and 95% confidence interval. All tests were 2-sided, with statistical significance predefined as a P value <0.05.

All statistical analyses were performed using R software version 4.0.2.

RESULTS

Patient characteristics

There were 328 patients in the cohort from January 2018 to August 2019. After excluding 7 patients due to missing data, 321 patients were included for analysis. Table 1 lists the patients' characteristics. Median age was 61.2 years and 82.9% were men. In terms of ethnicity, 62.6% were Chinese, 13.1% were Malay and 13.4% were Indian. Compared to Singapore Census of Population 2020 data (Chinese 74.3%, Malays 13.5%, Indians 9.0%), a larger proportion of our study cohort were Indians.

In total, 99 (30.8%) patients arrived by emergency ambulance and 222 (69.2%) arrived via own transport. Fig. 1 shows the study flow chart. Among the characteristics listed in Table 1, age, diabetes mellitus and smoking status was different between those arriving via emergency ambulance versus own transport.

Association between DTB timings, inpatient mortality and mode of transport

Fig. 2 shows that the median DTB time was shorter for patients arriving by emergency ambulance (52min, IQR 45–61) than by own transport (67 min, IQR 59–74, P<0.001). Further analysis showed that arrival via emergency ambulance was also associated with shorter median door-to-ECG time (11 min, IQR 5–15 vs 1 min, IQR 0–3; P<0.001) and door-to-activation (18 min, IQR 12–25 vs 2 min, IQR 0.10–7.50; P<0.001) (Table 2). There was no difference in inpatient mortality among patients arriving by emergency ambulance vs own transport (6.1% vs 2.7%, P=0.252)

DTB timings and prehospital measures

Table 3 shows median DTB time of patients based on whether they had prehospital ED standby, ECG transmission and CVL activation. Patients arriving via emergency ambulance without prehospital standby had a median DTB time of more than 60 minutes. With each additional measure (standby, prehospital ECG transmission and prehospital CVL activation), there was a trend towards shorter DTB times.

Other factors affecting various components of DTB time

Table 4 shows the results of multivariate adjustment for potential confounders (age, sex, office hours arrival). Usage of emergency ambulance remained significantly associated with shorter DTB time (18.5% shorter, 95% CI -22.3% to -14.5%, P<0.001), largely attributable to decreased door-to-ECG (87.7% shorter, 95% CI -91.7% to -81.8%, P<0.001) and door-to-CVL activation times (90.6% shorter, 95% CI -93.6% to -86.2%, P<0.001). Presentation during office hours was also significantly associated with shorter DTB time (8.5% shorter, 95% CI -12.5% to -4.3%, P<0.001), largely attributable to decreased time from arrival

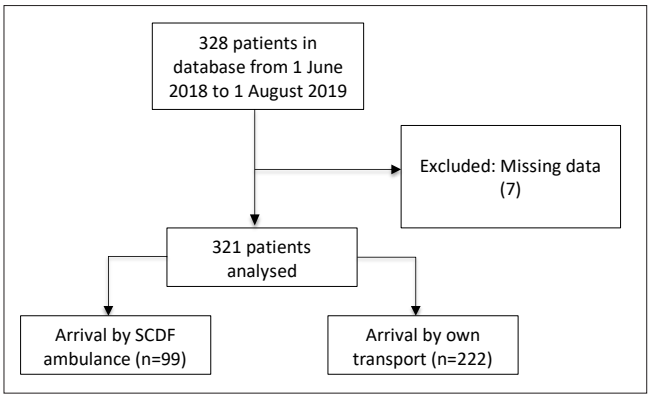


Fig. 1. Study flow chart.
SCDF: Singapore Civil Defence Force

at CVL lab to balloon inflation (21.1% shorter, 95% CI -28.3% to -13.2%, $P<0.001$)

DISCUSSION

Emergency ambulance usage and DTB time

In this study, we found that arrival via emergency ambulance was associated with DTB times roughly 15 minutes shorter than arriving via other modes of transport.

Prior studies have found that prehospital ECG transmission and CVL activation reduces DTB time. A nationwide, before- after-study in Singapore, showed a reduction of DTB time of 24 minutes after

Table 1. Characteristics of patients

Characteristics	Own transport (n=222) No. (%)	Emergency ambulance (n=99) No. (%)	*P* value
Man	182 (82.0)	90 (90.9)	0.059
Age, mean (SD), years	62.47 (11.01)	58.98 (11.85)	0.011
Race			0.085
Chinese	147 (66.2)	54 (54.5)	
Malay	26 (11.7)	16 (16.2)	
Indian	31 (14.0)	12 (12.1)	
Others	18 (8.3)	17 (17.1)	
Office-hours presentation	81 (36.5)	45 (45.5)	0.163
Day of the week			0.152
Monday	31 (14.0)	10 (10.1)	
Tuesday	35 (15.8)	16 (16.2)	
Wednesday	30 (13.5)	13 (13.1)	
Thursday	26 (11.7)	16 (16.2)	
Friday	29 (13.1)	21 (21.2)	
Saturday	37 (16.7)	7 (7.1)	
Sunday	34 (15.3)	16 (16.2)	
Diabetes mellitus	78 (35.3)	20 (21.1)	0.017
Hypertension	123 (55.7)	46 (48.4)	0.289
Dyslipidaemia	128 (57.9)	47 (49.5)	0.207
Current smoker	72 (32.6)	43 (45.3)	0.043
Prior myocardial infarction	23 (10.4)	8 (8.4)	0.735
Cerebrovascular disease	10 (4.5)	3 (3.2)	0.761
Peripheral arterial disease	5 (2.3)	1 (1.1)	0.672
Current dialysis	4 (1.8)	1 (1.1)	1

SD: standard deviation

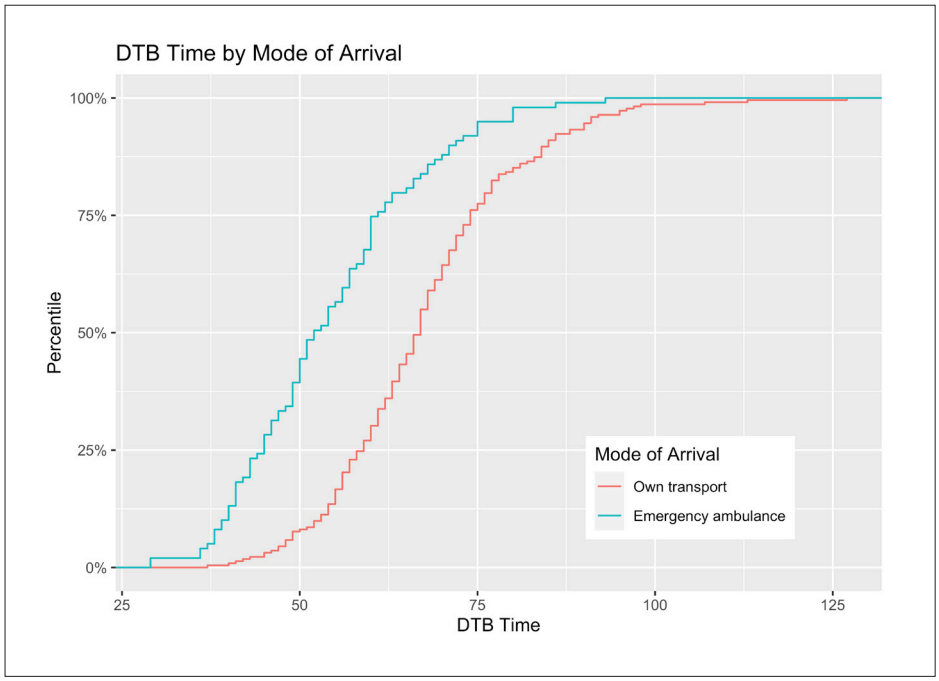


Fig. 2. DTB time by mode of arrival.
DTB: door-to-balloon

Table 2. Door-to-balloon (DTB) parameters and mortality by mode of arrival

DTB parameters	Own transport (n=222)	Emergency ambulance (n=99)	*P* value
DTB time, median (IQR), min	67.00 (59.00–74.00)	52.00 (45.00–60.50)	<0.001
DTB time <60 min, no. (%)	67 (30.2)	74 (74.7)	<0.001
DTB time <90 min, no. (%)	210 (94.6)	98 (99.0)	0.124
Deceased during stay, no. (%)	6 (2.7)	6 (6.1)	0.252
Door-to-ECG time, median (IQR), min	11.00 (5.00–15.00)	1.00 (0–3.00)	<0.001
Door-to-CVL activation time, median (IQR), min	18.00 (12.00–25.00)	2.00 (0.10–7.50)	<0.001
CVL activation to CVL arrival, median (IQR), min	29.00 (25.00–33.00)	30.00 (25.00–36.00)	0.178
CVL arrival to balloon, median (IQR), min	19.00 (14.00–24.00)	17.00 (13.00–22.75)	0.126

CVL: cardiovascular laboratory; ECG: electrocardiogram; IQR: interquartile range

Table 3. Door-to-balloon (DTB) time for various prehospital factors

Prehospital factor	DTB time, median (IQR), min
Arriving via own transport (n=222)	67.00 (59.00–74.00)
Arriving via SCDF but ED not put on standby (n=7)	62.00 (58.00–71.50)
Arrived via SCDF, ED put on standby but no ECG transmitted (n=37)	54.00 (44.00–67.00)
Arrived via SCDF, ED put on standby, ECG transmitted but no prehospital activation (n=15)	51.00 (45.50–60.00)
Arrived via SCDF, ED put on standby, ECG transmitted with prehospital activation (n=40)	51.00 (43.00–57.25)

ECG: electrocardiogram; ED: emergency department; IQR: interquartile range; SCDF: Singapore Civil Defence Force

Table 4. Variables associated with change in components of door-to-balloon time after adjustment for confounders

	Ambulance usage (95% CI)	***P* value**
Door-to-balloon time	18.5% shorter (-22.3 to -14.5%)	**<0.001**
Door-to-ECG time	87.7% shorter (-91.7 to -81.8%)	**<0.001**
Door-to-activation time	90.6% shorter (-93.6 to -86.2%)	**<0.001**
Activation-to-lab time	10.5% longer (-2.5 to 25.5%)	0.12
Lab-to-balloon time	6.2% shorter (-15.2 to 3.8%)	0.22
	Office-hours presentation (95% CI)	***P* value**
Door-to-balloon time	8.5% shorter (-12.5 to -4.3%)	**<0.001**
Door-to-ECG time	1.5% longer (-29.6 to 46.2%)	0.93
Door-to-activation time	1.4% shorter (-31.1 to 41.1%)	0.94
Activation-to-lab time	9.7% shorter (-19.8 to 1.64%)	0.09
Lab-to-balloon time	21.1% shorter (-28.3 to -13.2%)	**<0.001**

CI: confidence interval; ECG: electrocardiogram
P values in bold are significant

implementation of out-of-hospital ECG recording and transmission.[9] Another study by Rao et al. showed that mean DTB time for patients was reduced from 90.5 to 60.2 minutes when ECG was transmitted prehospital.[8] In both studies, prehospital CVL activation was done if STEMI was diagnosed on the transmitted ECG prior to hospital arrival.

As such capabilities are only available to patients arriving by emergency ambulance, this might account for some of the reduction in DTB time that our study has identified. The main timings impacted by mode of transport relate to processes within the ED such as obtaining an ECG, with no impact on timings after CVL activation. This suggests that there are workflows within the ED pertaining to the patients arriving via emergency ambulance that allow for speedier CVL activation, and deeper analysis of the processes might identify potential areas of improvement for patients arriving via own transport. Notably, a prior study by Lee et al. has suggested that door-to-ECG time is a key in reducing DTB time.[17] In their study, they achieved a median door-to-ECG time of 5 minutes for walk-in patients.

Low rates of emergency ambulance usage

Our study population had a low proportion of STEMI patients who arrived via emergency ambulance. Compared to an emergency ambulance usage rate of 50–60% reported by national and international studies,[11,12] our study population had an ambulance usage rate of 30.8%. This could be due to the National Heart Centre Singapore being co-located with our hospital. Existing patients on follow-up with the specialist centre as well as patients who wish to be treated there might opt to be transported via their own transport, as there is public awareness that emergency ambulances do not allow users to choose their destination, and always convey patients to the nearest hospital. This is an area that would benefit from public education campaigns on the appropriate usage of ambulances.

Other factors affecting DTB time

When we analysed other factors that impacted various components of DTB time, we noted that presentation after hours was associated with a longer DTB time, which was largely related to longer timings after activation of CVL. This is in agreement with a large prospective observational study in England, which showed that after-hours admission was associated with a longer DTB time.[16] Our findings are unique as we were able to break down the components of DTB time to see which aspect was impacted. Based on our findings, we recommend that departments looking to improve after-hours DTB times focus on the processes after CVL lab activation such as movement of patients to the CVL as well as the call-back process for on-call CVL personnel.

Further research

Three areas would benefit from further research. Firstly, exploring the reasons behind a patient's choice of transport to the hospital would guide the crafting and delivery of public education campaigns. For example, a lack of awareness might have contributed to a patient's decision to call an ambulance, and further research would help us understand the extent of this problem. Secondly, deeper analysis of the PCI process in the hospital might identify the reasons for the slower door-to-ECG time we identified among patients who came via their own transport. Lastly, further studies on the impact of reduced DTB time on long-term outcomes of the patients should be conducted.

Limitations

This was not a randomised trial, and thus certain factors such as presenting complaint or patient comorbidity could have served as confounders. However, as inclusion in the database required clear-cut ECG changes of STEMI and the presence of symptoms, we believe that this should have a fairly small effect.

Secondly, in our institution, the patient's arrival time (first time stamp) is created upon scanning their identification at the screening area. For patients arriving by ambulance, this is done concurrently by the paramedics while the patient receives care (e.g. ECG, assessment). For these cases, if the ECG time was before the registration time, we recorded an ECG time of 0 minute (ECG on arrival). This might represent a source of bias if the patient had delayed ECG but had an even more delayed registration. We think this is unlikely to present a large bias, as the registration process in our institution is electronic, and unlikely to cause a long delay.

Thirdly, the SCDF ECG database might not be complete, as for some cases, the prehospital ECG might be transmitted prior to identification of the patient. Subsequently, when the patient has been identified and registered in the hospital, this prehospital ECG is not linked retrospectively. As such, some of the cases that were deemed not having a prehospital ECG might have actually had one. We tried to mitigate this by a medical record review as physicians document prehospital ECG interpretation and CVL activation.

Fourthly, we did not have information on the patients' clinical presentations, STEMI types, or long-term follow-up. While the entire cohort had to present with ECG changes and symptoms before being included, patients with very typical symptoms might opt for ambulance use, while others with milder/atypical symptoms might opt for their own transport. More subtle ECG changes might also affect the decision by the provider to activate the CVL. These might be sources of bias. Also, while we did not detect a difference in inpatient mortality, outcome differences might be present on long-term follow-up.

Lastly, while we were able to identify certain aspects of DTB time that was affected by mode of transport and time of arrival, the process of CVL activation is unique to every institution and thus the findings might not be generalisable. However, such a framework for studying the process can still serve as a guidance to other institutions looking to improve their DTB times.

CONCLUSION

For patients with STEMI undergoing PCI, arriving via emergency ambulance is associated with shorter DTB time. Mechanisms such as prehospital ECG transmission and CVL activation could contribute to this, but processes within the ED also account for part of the reduction in DTB time. Considering that only a third of patients with STEMI arrive via emergency ambulance, public education is sorely needed to increase awareness of STEMI symptoms and to utilise emergency transportation when experiencing those symptoms. Further studies that look into the various processes in detail would be useful to guide measures and workflows to improve DTB time, especially for walk-in patients and patients who present after hours.

REFERENCES

1. De Luca G, Suryapranata H, Ottervanger JP, et al. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation 2004;109:1223-5.
2. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2006;47:2180-6.
3. Rathore SS, Curtis JP, Chen J, et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. BMJ 2009;338:b1807.
4. Carville S, Harker M, Henderson R, et al, on behalf of the Guideline Development Group. Acute management of myocardial infarction with ST-segment elevation: summary of NICE guidance. BMJ 2013;347:f4006. Erratum in 2021:372:m4946.
5. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the management of patients with non–ST-Elevation acute coronary syndromes. J Am Coll Cardiol 2014 64:e139-228.
6. Chen FC, Lin YR, Kung CT, et al. The association between door-to-balloon time of less than 60 minutes and prognosis of patients developing ST segment elevation myocardial infarction and undergoing primary percutaneous coronary intervention. BioMed Res Int 2017;2017:1-6.
7. National Registry of Diseases Office, Singapore. Singapore Myocardial Infarction Registry Annual Report 2007-2018. Available at: https://www.nrdo.gov.sg/publications/ami. Accessed on 20 January 2021.

8. Rao A, Kardouh Y, Darda S, et al. Impact of the prehospital ECG on door-to-balloon time in ST elevation myocardial infarction. Cathet Cardiovasc Intervent 2010;75:174-8.
9. Ong ME, Wong AS, Seet CM, et al. Nationwide improvement of door-to-balloon times in patients with acute ST-Segment elevation myocardial infarction requiring primary percutaneous coronary intervention with out-of-hospital 12-lead ECG recording and transmission. Ann Emerg Med 2013;1:39-47.
10. Savage ML, Poon KK, Johnston EM, et al. Pre-Hospital ambulance notification and initiation of treatment of ST elevation myocardial infarction is associated with significant reduction in door-to-balloon time for Primary PCI. Heart Lung Circ 2014;23:435-43.
11. So DY, Ha AC, Turek MA, et al. Comparison of mortality patterns in patients with ST-elevation myocardial infarction arriving by emergency medical services versus self-transport (from the Prospective Ottawa Hospital STEMI Registry). Am J Cardiol 2006;97:458-61.
12. Ho AF, Loy EY, Pek PP, et al. Emergency medical services utilization among patients with ST-Segment elevation myocardial infarction: Observations from the Singapore Myocardial Infarction Registry. Prehosp Emerg Care 2016;20:454-61.
13. Singapore Civil Defence Force. Annual report. Available at: https://www.scdf.gov.sg/home/about-us/media-room/publications/annual-reports. Accessed on 18 December 2020.
14. Emmanuel SC, Tan AT, Tunstall-Pedoe H, et al. The operational research study for the Singapore Myocardial Infarction Register. Singapore Med J 1988;29:446-57.
15. Pilgrim T, Heg D, Tal K, et al. Age- and gender-related disparities in primary percutaneous coronary interventions for acute ST-segment elevation myocardial infarction. PLoS ONE 2015;10:e0137047.
16. Jayawardana S, Salas-Vega S, Cornehl F, et al. The relationship between off-hours admissions for primary percutaneous coronary intervention, door-to-balloon time and mortality for patients with ST-elevation myocardial infarction in England: a registry-based prospective national cohort study. BMJ Qual Saf 2020;29:541-9.
17. Lee CK, Meng SW, Lee MH, et al. The impact of door-to-electrocardiogram time on door-to-balloon time after achieving the guideline-recommended target rate. PLoS ONE 2019;14:e0222019.

ORIGINAL ARTICLE

Ann Acad Med Singap 2021;50:679-85
https://doi.org/10.47102/annals-acadmedsg.2020635

Strategies for a successful hepatic artery anastomosis in liver transplantation: A review of 51 cases

Bien-Keem Tan [1]*FRCS*, Hui Chai Fong [1]*MRCS*, Ek-Khoon Tan [2]*FRCS*, Jeyaraj Prema Raj [2,3]*FRCS*

ABSTRACT

Introduction: Hepatic artery reconstruction is a critical aspect of liver transplantation. The microsurgeon faces several challenges when reconstructing the hepatic artery—the donor hepatic artery stalk is short and often a poor match for the usually hypertrophic recipient vessels. Previous inflammation impedes vessel dissection, and recipient vessels have a tendency to delaminate with manipulation. We review 51 consecutive liver transplantations to highlight these problems and propose strategies for a successful reconstruction of the hepatic artery.

Methods: A prospective study involving all adult patients undergoing liver transplantation at the Singapore General Hospital from January 2015 to December 2018 was undertaken. All hepatic artery anastomoses were performed by 2 microsurgeons at 10x magnification. Patients were started on a standard immunosuppressive regimen. Postoperative ultrasound scans on days 1, 3, 5, 7, 9 and 14 were used to confirm arterial patency.

Results: There were 51 patients who underwent liver transplantation during the study period. Of this number, 31 patients received deceased donor grafts and 20 received living donor grafts. A total of 61 anastomoses were performed (5 dual anastomosis, 4 radial artery interposition grafts) with 1 case of hepatic artery thrombosis that was successfully salvaged. The mean (range) postoperative resistive index and hepatic artery peak systolic velocity were 0.69 (0.68–0.69) and 1.0m/s (0.88–1.10m/s), respectively.

Conclusion: Hepatic artery thrombosis after liver transplantation is poorly tolerated. The challenges of hepatic artery reconstruction in liver transplantation are related to vessel quality and length. The use of microsurgical technique, appropriate recipient vessel selection, minimisation of vessel manipulation with modified instruments, variation in anastomosis techniques, and use of radial artery interpositional grafts are useful strategies to maximise the chances of success.

Ann Acad Med Singap 2021;50:679-85

Keywords: Hepatic artery, hepatology, liver transplant, microsurgery, plastic surgery

INTRODUCTION

Liver transplantation is a life-saving procedure for patients with chronic end-stage liver disease, and selected patients with acute liver failure. While 75% of total blood flow into the liver comes from the portal vein, the sole supply of oxygenated blood to the biliary system comes from the hepatic artery.[1] A patent hepatic arterial anastomosis is critical in liver transplantation as thrombosis can result in ischaemia of the bile duct, presenting as biliary leak and resulting in eventual liver failure. Hepatic artery thrombosis leads to retransplantation in 50–75% of patients, with a mortality rate approaching 50%.[2]

While the introduction of microsurgical techniques has been instrumental in decreasing the rate of hepatic artery thrombosis, the microsurgeon faces unique challenges when reconstructing the hepatic artery. Firstly, the donor hepatic artery stalk is short, and of small calibre, mismatching with the recipient vessels. Secondly, previous peritonitis may render the coeliac axis fibrotic, impeding vessel dissection. Thirdly, a high proportion of patients undergoing liver transplantation have liver steatosis and atherosclerosis, or vessels that have been subjected to transarterial chemoembolisation (TACE),

[1] Department of Plastic, Reconstructive and Aesthetic Surgery, Singapore General Hospital, Singapore
[2] Department of Hepato-pancreato Biliary Surgery, Singapore General Hospital, Singapore
[3] SingHealth Duke-NUS Transplant Centre, Singapore
Correspondence: Prof Bien-Keem Tan, Department of Plastic, Reconstructive and Aesthetic Surgery, Singapore General Hospital, Outram Road, Singapore 169608.
Email: tan.bien.keem@singhealth.com.sg

CLINICAL IMPACT

What is New

- The challenges in hepatic artery reconstruction in liver transplantation are related to a mismatch in vessel size between donor and recipient hepatic arteries, and poor quality of recipient vessels.
- A multispecialty approach using modified operating instruments, meticulous microsurgical operating techniques, and interpositional arterial grafts can help maximise the long-term patency of the reconstructed hepatic artery.

Clinical Implications

- These solutions are particularly applicable to patients in Singapore, whose recipient vessels tend to be smaller and are more affected by previous transarterial interventions or atherosclerosis.

resulting in vessel walls that are fragile (Fig. 1). In this series of 51 patients, we aim to highlight these challenges and discuss our surgical strategies for a successful anastomosis.

METHODS

A review was conducted of all adult patients who underwent deceased or living donor liver transplantation at the Singapore General Hospital from January 2015 to December 2018. All hepatic artery anastomoses were performed with the aid of an operating microscope by 2 surgeons. Demographic and operative data collected were age, indication for transplantation, type of transplantation, artery calibre and recipient vessel. Outcome data collected were postoperative hepatic artery resistive indices and peak systolic velocities at postoperative days 1, 3, 5, 7, 9 and 14, and any occurrence of biliary leak or hepatic artery thrombosis was recorded. Patients were on a standardised immunosuppression regimen in accordance with the department liver transplant protocol.

Surgical technique

Following hepatectomy and inset of the donor liver, the liver transplant surgeons proceeded with reconstitution of the hepatic vein and portal vein. This was followed by anastomosis of the hepatic artery by the plastic surgery team, and subsequent biliary reconstruction by the transplant team. The operating microscope, positioned at the patient's left, was used for all hepatic artery anastomosis. Utilising a moist penny towel and a Thompson retractor, the donor liver was retracted superiorly to expose the recipient vessels. A second assistant, standing at the patient's left side, manually retracted any protrusive loops of bowel with a moist penny towel. Vessel preparation and anastomosis were performed at 10x magnification. To obtain a linear arteriotomy, the recipient vessel was supported on an angled cutting platform, and an 11 blade, mounted on an angled blade holder, was used to trim/incise the vessel. The vessel edge was freshened (but not skeletonised) before the arterial wall was coapted in 2 layers. The sutures used for anastomosis were 8/0, and the repair was reinforced with interrupted 9/0 adventitial stitches. Fibrin sealant was applied over the anastomosis to reinforce the watertight seal and also to fix the lie of the vessel. Intraoperative duplex ultrasound was used to confirm patency of the anastomosis.

RESULTS

There were 51 patients who underwent liver transplantation (Table 1). The mean (range) age was 58 (41–71) years and 69% of the patients were men (n=35). The most common indications were chronic hepatitis, non-alcoholic steatohepatitis and primary biliary cirrhosis.

There were 31 patients who received deceased donor liver grafts (DDLT) and 20 received living donor liver grafts (LDLT). The mean DDLT graft weight was 1,353.3g, while the mean LDLT graft weight was 570.5g. The most common recipient artery was the left or right hepatic artery (n=31), followed by the common hepatic artery (n=10) and gastroduodenal artery (n=4). Dual anastomoses were performed in 5 cases and radial artery interpositional grafts utilised in 4 cases. An end-to-end anastomosis was performed by default; an end-to-side technique was employed in 2 cases due to calibre mismatch. The average time for a single arterial anastomosis was 75min. The mean (range) postoperative resistive index and hepatic artery peak systolic velocity were 0.68m/s (0.68–0.79) and 0.98m/s (0.86–1.06). One patient developed hepatic artery thrombosis on postoperative day 5. This was detected on ultrasound surveillance, confirmed on computed tomographic angiography, and successfully salvaged with arterial thrombectomy and the use of a radial artery interpositional graft. During the study period, 3 patients died from unrelated causes (sepsis: n=2, 9 months and 22 months post-transplant; recurrent hepatocellular carcinoma: n=1, 7 months post-transplant). Two patients developed postoperative biliary stenosis that was successfully treated with biliary stenting. In both cases, ultrasound sonography showed

Table 1. Patient demographics

Characteristics	N=51
Sex	
Female	16
Male	35
Age	
Age, mean (range), years	58 (41–71)
Diagnosis	
Hepatitis B or C	23
Non-alcoholic steatohepatitis	11
Primary biliary cirrhosis	5
Hepatocellular carcinoma	4
Alcoholic liver disease	3
Others	5
Transplant type	
Living donor grafts	18
Deceased donor liver grafts	31
Graft weight, mean, g	
Living donor grafts	570
Deceased donor liver grafts	1353

Table 2. Outcome data recorded

Complications	No. of patients
Hepatic artery thrombosis	1[a]
Biliary stenosis	2[b]
Mortality	
Sepsis	2[c]
Recurrent hepatocellular carcinoma	1[d]
Postoperative day number	**Peak systolic velocity, mean (range), m/s**
1	1.06 (0.15–3.12)
3	0.86 (0.20–3.05)
5	0.95 (0.28–2.36)
9	1.00 (0.23–2.13)
14	1.06 (0.15–3.12)
Postoperative day number	**Resistive index, mean (range)**
1	0.68 (0.33-0.97)
3	0.69 (0.30–0.97)
5	0.69 (0.41–0.84)
9	0.69 (0.40–0.82)
14	0.69 (0.45–0.88)

[a] postoperative day 5, salvaged
[b] hepatic artery Doppler ultrasound normal
[c] 9 months and 22 months post-transplant
[d] 7 months post-transplant

normal resistive indices and triphasic intrahepatic arterial flow, indicating patency of the hepatic artery anastomosis (Table 2).

DISCUSSION

In this series of 51 patients, we draw special attention to the microsurgical challenges of hepatic artery reconstruction in liver transplantation. The problems related mainly to vessel adequacy (length, calibre and thickness mismatch) and vessel quality (vessel fibrosis and a preponderance for intimal separation).

Problem 1: Calibre and thickness mismatch

Some degree of vessel mismatch is always anticipated as patients with liver cirrhosis develop hypertrophy of the coeliac axis from chronic portal hypertension. The difficulties of working with a short vessel stump, particularly with LDLT, are compounded by the deep cavity wherein the recipient vessels reside.

The ideal recipient artery should have adequate length, minimal fibrosis and a good pressure head. The left or right hepatic artery is our first choice. Arising from the bifurcation of the proper hepatic artery at or just proximal to the porta hepatis, the mean diameter of these vessels in our study population was 2.3mm, making them a good size match for donor vessels up to the level of the proper hepatic artery. For larger calibre donor vessels, the bifurcation of the left and right hepatic arteries at the proper hepatic artery, or the take-off of the splenic artery can be used.

If the hepatic arteries are fibrotic or delaminated, the coeliac axis offers several alternatives. The common hepatic artery, arising from the coeliac axis, runs superolaterally along the upper border of the pancreas to the left side of the portal vein, before splitting into the gastroduodenal artery and the proper hepatic artery. With a mean diameter of 4.2mm, the common hepatic artery is useful if the donor pedicle is large, with some redundancy. In our series, it was used in DDLT (n=10), where the donor graft was procured at the level of the coeliac trunk or common hepatic artery, or in conjunction with the gastroduodenal artery as part of a dual anastomosis (n=3).

The gastroduodenal artery is a useful option in patients who have undergone transarterial chemoembolisation as these vessels are spared during treatment. It can also be used in conjunction with the common hepatic artery in a dual anastomosis configuration (n=3) for large grafts. A branch of the common hepatic artery, it passes inferiorly towards the first part of the duodenum, and bifurcates into the right gastroepiploic and superior pancreaticoduodenal artery. The mean diameter of the gastroduodenal artery was 3.2mm in our series. If a larger calibre is required, the bifurcation of the gastroduodenal artery at the common hepatic artery is the preferred location for the anastomosis. The vessel should be prepared carefully as aggressive dissection can cause injury or devascularisation of the pancreatic head.

Other recipient vessels that have been employed included the right gastroepiploic artery[3] and the distal abdominal aorta (in conjunction with a donor iliac artery vascular graft).[4] If the donor stump is small but of sufficient length, end-to-side anastomosis can be performed to overcome calibre mismatch. A slit arteriotomy is used, in contrast with a traditional excision type arteriotomy, as it is mechanically advantageous[5] and minimises vessel manipulation.

Problem 2: Short vessel stump

In the situation where vessel size and length are inadequate, a radial artery interpositional graft is used as a vascular funnel. With a mean diameter of 4mm, it serves as a bridge between donor recipient vessels that are severely mismatched (Fig. 2) while allowing for a tension-free anastomosis. Preoperatively, previous percutaneous vascular interventions (intra-arterial blood pressure monitoring, access for coronary angioplasty) should be noted and Allen's test performed.

The radial artery is palpated or traced using Doppler scanning along its axis, just deep to the flexor carpi radialis (FCR). Under tourniquet control, a 5cm incision is made on the radial forearm. The FCR is retracted radially to expose the radial artery and a 5–8cm segment is harvested. The graft is clamped proximally and flushed through with heparinised saline to check for leaks before the distal anastomosis, at the donor graft, is performed on the back table. In our series, radial artery interpositional grafts were used in 4 cases of LDLT in an end-to-end configuration. In 3 patients, artery grafting was performed primarily to overcome a short donor stump, while in 1 patient who underwent previous TACE, it was performed as a secondary procedure following the development of hepatic artery thrombosis on postoperative day 5.

The use of saphenous[6] and common iliac vein grafts[7] have been reported, but they have been associated with thrombosis rates of up to 23.8%.[8] Moreover, in our estimation, arterial grafts were a better match for the hepatic artery as vein grafts were less suited for the transmission of high arterial pressures.

Problem 3: Poor recipient vessel quality

Due to previous transarterial chemoembolisation, peritonitis or atherosclerosis, the recipient vessels of patients undergoing liver transplantation are fragile, with a tendency to tear or delaminate with manipulation.

To preserve vessel integrity, handling of the adventitia and vessel skeletonising should be minimised during preparation. This process is greatly facilitated with the use of angled instruments (Fig. 3). The vessel is positioned on a cutting platform that is fashioned from a 60-degree angulated steel blade. The microsurgical assistant steadies this buttress while the primary surgeon uses an 11 blade, mounted at a similar angle, to incise the vessel edge in a guillotine fashion. Unlike reusable instruments, the edge of the disposable blade is guaranteed, producing a crisp, uniform vessel edge in a single pass, with minimal disruption of the intima.

Anastomotic techniques specific to hepatic artery reconstruction

Anastomotic leak is poorly tolerated as the underlying coagulopathy and high driving pressures across the anastomosis may herald postoperative haematoma. We have modified our suture technique to minimise anastomotic leak.

Far and near stitching

A staggered stitching technique was employed in vessels that have previously undergone chemoembolisation. Due to excessive friability, a linear line of perforations in the vessel wall has a tendency to fissure (Fig. 4). To circumvent this, interrupted stitches were taken at varying distances from the vessel edge to produce a staggered suture line.

Intimal tagging

In cases where intimal dissection had occurred and further cutback of the vessel was not feasible, the intima was tagged down to the tunica media by passing the suture intraluminally to extraluminally, past the point of separation. If dissection had occurred in both donor and recipient vessels, a double arm suture was used, and the suture introduced intraluminally on both sides, directed past the area of delamination and thence through the vessel wall (Fig. 5).

Adventitial stitches

Following completion of the anastomosis with 8/0 or 9/0 suture, reinforcing 9/0 or 10/0 adventitial stitches were applied before the anastomosis was secured with application of fibrin sealant. These external stitches sealed any gaps which may only become evident following release of the vessel clamps.

Case examples

We discuss 4 case examples from our series.

Case 1: Living donor liver transplant

Problem: Short stump

Solution: Radial artery graft

A 71-year-old man with multifocal hepatocellular carcinoma (HCC) secondary to chronic hepatitis B and a model for end-stage liver disease (MELD) score of 20 underwent LDLT. The graft weight was 661g. The stump of the donor hepatic artery was 6mm, necessitating the use of a radial artery interposition graft in order for end-to-end anastomosis to the recipient common hepatic artery. The donor anastomosis was performed on a benchtop before the radial artery was anastomosed to the recipient common hepatic artery. Postoperatively, he developed a biliary anastomotic leak that was managed successfully with endoscopic stenting. Surveillance ultrasound confirmed patent arterial flow with normal resistive indices. He was discharged well 6 weeks postoperatively.

Case 2: Living donor liver transplant

Problem: Vessel mismatch

Solution: End-to-side anastomosis

A 63-year-old man with non-alcoholic steatohepatitis-induced cirrhosis and a MELD score of 18 underwent LDLT. A 3:1 size mismatch between the recipient left hepatic artery and donor common hepatic artery branch was noted, necessitating the use of end-to-side anastomosis technique. Postoperative duplex ultrasound showed patent inflow and normal resistive indices. He was discharged well on day 19 postoperatively (Fig. 6).

Case 3: Living donor liver transplant

Problem: Previous TACE with poor vessel quality; hepatic artery thrombosis

Solution: Salvage with radial artery graft

A 56-year-old man with recurrent HCC despite 4 previous sessions of transarterial chemoembolisation and radio frequency ablation underwent LDLT. A 2:1 mismatch in vessel size was overcome with standard microsurgical technique, and end-to-end anastomosis between the recipient left hepatic artery and donor right hepatic artery was performed. Initial postoperative

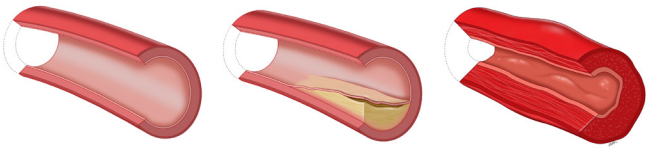


Fig. 1. Pathological condition of atherosclerotic and chemoembolised vessels. Centre: The presence of intimal plaque in atherosclerotic vessels results in a tendency for intimal separation. Right: Previous chemoembolisation renders vessels fibrotic with pan-vessel oedema and fragility.

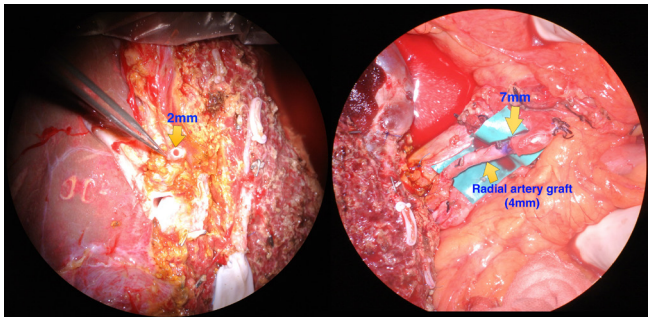


Fig. 2. The radial artery graft (4mm mean diameter) acts as a vascular funnel in cases of severe mismatch, while allowing for a tension-free anastomosis.

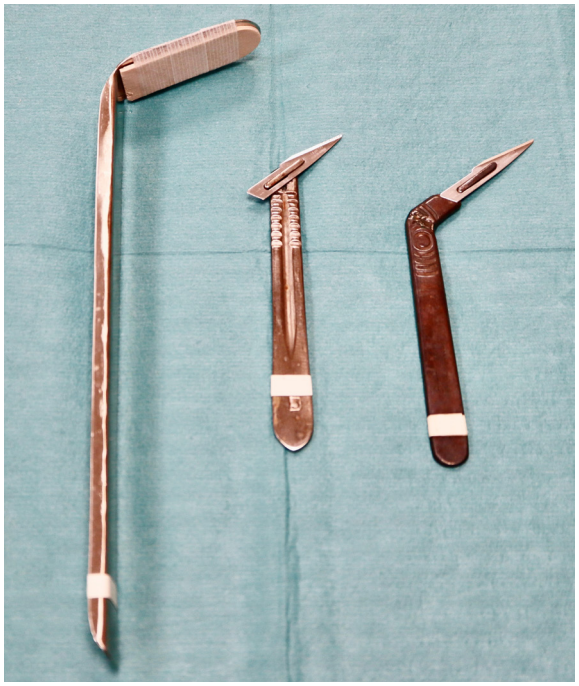


Fig. 3. Angled cutting platform. Angled instruments facilitate vessel preparation and the use of a disposable 11 blade guarantees a sharp cutting edge.

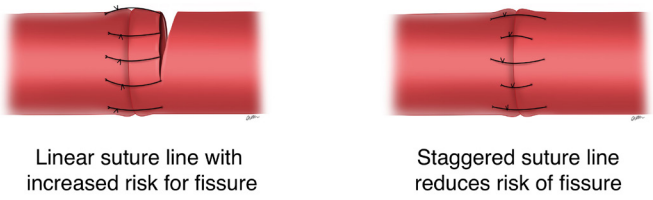


Fig. 4. Far-and-near stitching. Left: A linear line of sutures has a tendency to cause fissuring. Right: Interrupted stitches can be taken at variable distances from the vessel edge to create a staggered suture line.

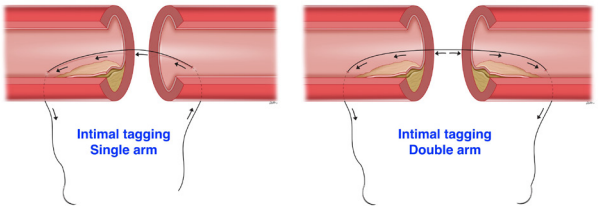


Fig. 5. Intimal tagging sutures. Left: The suture is taken past the point of delamination to tag it down to the tunica media. Right: If both recipient and donor vessels have delaminated, a double arm suture is used.

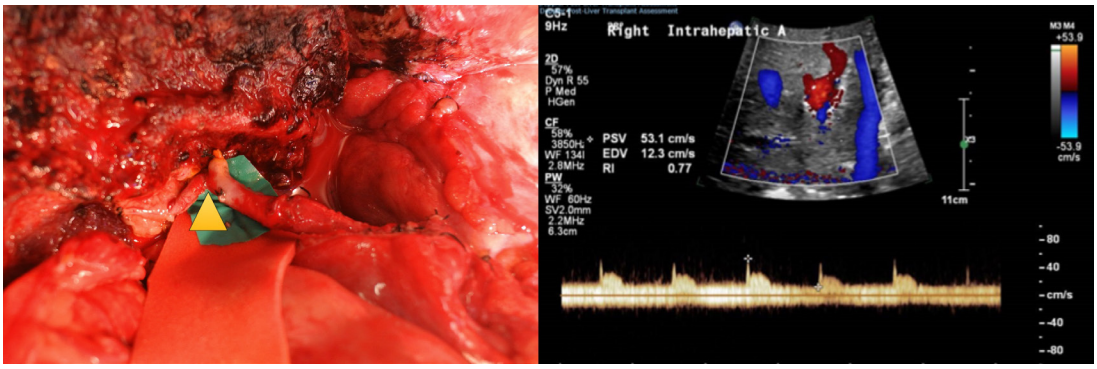


Fig. 6. Living donor liver transplant. Intraoperative photograph showing how a 3:1 vessel calibre mismatch between the recipient left hepatic artery and donor common hepatic artery was overcome. Left: An end-to-side anastomosis was performed. Right: Postoperative ultrasonography showed good flow with a resistive index of 0.77.

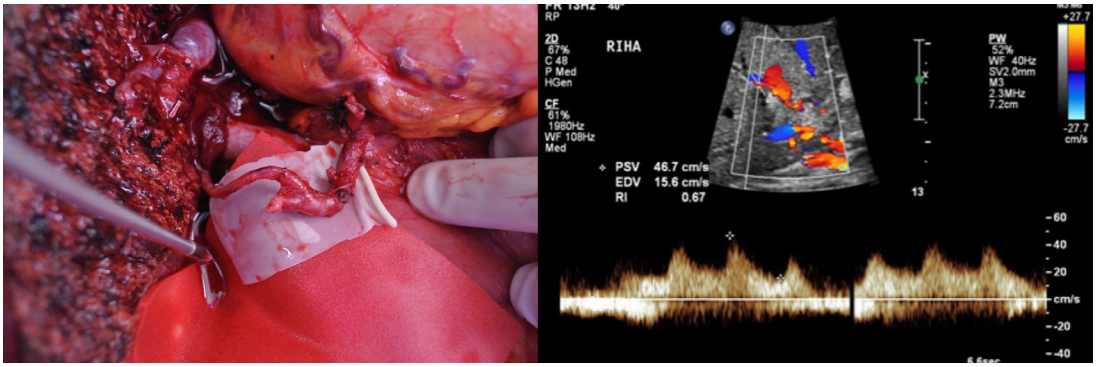


Fig. 7. Living donor liver transplant in a patient with previous transarterial chemoembolisation and radiofrequency ablation. Left: Anastomotic thrombosis was salvaged with an interpositional radial artery graft on postoperative day 5. Right: Post-salvage ultrasonography showed good flow with a resistive index of 0.67.

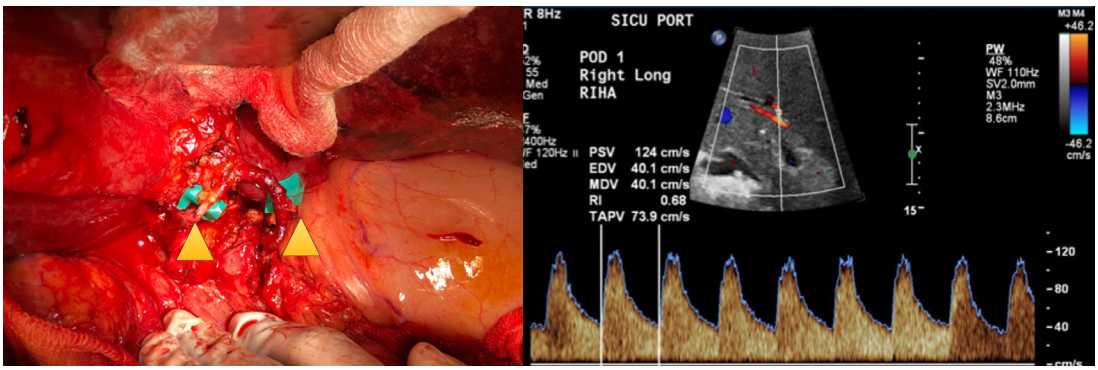


Fig. 8. Deceased donor liver transplant using a large donor liver (1,500g). Two separate inflows were created to improve global perfusion. Left: The main inflow was through the common hepatic artery (right arrow), and a second inflow created through the gastroduodenal artery (left arrow) supercharged the graft. Right: The postoperative ultrasonography showed good flow with a resistive index of 0.68.

Doppler ultrasound showed a downtrending resistive index of 0.62–0.53. On postoperative day 5, the hepatic arteries were not identifiable on Doppler ultrasound. A computed tomography (CT) angiogram confirmed complete thrombosis of the hepatic artery. On investigation, it was found that the posterior vessel wall had delaminated during placement of the posterior stitch. Following unsuccessful balloon thrombectomy, the decision was made to use the gastroduodenal artery with a radial artery interposition graft. CT angiography on day 16 post-revision confirmed a patent anastomosis with enhancement of small calibre intrahepatic arteries. The patient was transferred to a rehabilitation hospital 1 month postoperatively (Fig. 7).

Case 4: Deceased donor liver transplant

Problem: Large graft size (>1,000g)

Solution: Dual anastomosis

A 60-year-old woman with acute on chronic hepatitis B flare and fulminant liver failure underwent DDLT. The donor graft was 1,583g. In view of the significant size of the graft, dual end-to-end anastomosis between the right hepatic artery to the recipient gastroduodenal artery, and left hepatic artery to the recipient common hepatic artery was performed. Postoperative Doppler ultrasound showed patent intrahepatic arterial flow and normal resistive indices. The patient was discharged well on day 21 postoperatively (Fig. 8).

CONCLUSION

Hepatic artery thrombosis after liver transplantation is poorly tolerated with high morbidity and mortality. The challenges of hepatic artery reconstruction in liver transplantation are related to vessel quality and adequacy. Recipient vessel selection, radial artery interpositional grafts, selective vessel manipulation and variations in anastomosis technique are useful strategies to maximise the chances of success.

REFERENCES

1. Northover J, Terblanche J. Bile duct blood supply. Its importance in human liver transplantation. Transplantation 1978;26:67-9.
2. Imagawa DK, Busuttil RW. Technical problems: vascular. In: Busuttil RW, Klintmalm GB. Transplantation of the liver, 2nd ed. Pennsylvania: WB Saunders; 2005.
3. Ikegami T, Kawasaki S, Hashikura Y, et al. An alternative method of arterial reconstruction after hepatic arterial thrombosis following living-related liver transplantation. Transplantation 2000; 69:1953-5.
4. Shaw BW Jr, Iwatsuki S, Starzl TE. Alternative methods of arterialization of the hepatic graft. Surg Gynecol Obstet 1984; 159:490-3.
5. Tan BK, Wong CH, Chew W, Hong SW. Use of the slit arteriotomy for end-to-side arterial anastomosis in free-tissue transfers to the extremities. J Plast Reconstr Aesthet Surg 2009;62:1519-23.
6. Garcia-Valdecasas JC, Grande L, Rimola A, et al. The use of the saphenous vein for arterial reconstruction in orthotopic liver transplant. Transplant Proc 1990;22:2376-7.
7. Asakura T, Ohkohchi N, Orii T, Koyamada N, et al. Arterial reconstruction using vein graft from the common iliac artery after hepatic artery thrombosis in living-related liver transplantation. Transplant Proc 2000;32:2250-1.
8. Tzakis AG, Gordon RD, Shaw BW Jr, et al. Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporin era. Transplantation 1985;40:667-71.

ORIGINAL ARTICLE

Ann Acad Med Singap 2021;50:686-94
https://doi.org/10.47102/annals-acadmedsg.2021129

Association between lung compliance phenotypes and mortality in COVID-19 patients with acute respiratory distress syndrome

Ser Hon Puah [1]*MRCP (UK)*, Matthew Edward Cove [2,12]*MBChB (UK)*, Jason Phua [2,3]*FRCP (Edin)*, Amit Kansal [4]*FCICM (Aus & NZ)*, Jonathen Venkatachalam [5]*MRCP (UK)*, Vui Kian Ho [6]*FANZCA (Anaes)*, Duu Wen Sewa [7]*MRCP (UK)*, Roshni Sadashiv Gokhale [8]*MRCP (UK)*, Mei Fong Liew [2,3]*MMed (Int Med)*, Benjamin Choon Heng Ho [1]*MRCP (UK)*, Jensen Jiansheng Ng [9]*MMed (Anaes)*, John A Abisheganaden [1,10]*FRCP (Edin)*, Yee Sin Leo [10,11,12,13,14]*FRCP*, Barnaby Edward Young [10,11,12]*DLSHTM*, David Chien Lye [10,11,12,13]*FRCP (UK)*, Tsin Wen Yeo [10,11,12]*PhD*, on behalf of Singapore 2019 Novel Coronavirus Outbreak Research Team

ABSTRACT

Introduction: Acute respiratory distress syndrome (ARDS) in COVID-19 is associated with a high mortality rate, though outcomes of the different lung compliance phenotypes are unclear. We aimed to measure lung compliance and examine other factors associated with mortality in COVID-19 patients with ARDS.

Methods: Adult patients with COVID-19 ARDS who required invasive mechanical ventilation at 8 hospitals in Singapore were prospectively enrolled. Factors associated with both mortality and differences between high (<40mL/cm H_2O) and low (<40mL/cm H_2O) compliance were analysed.

Results: A total of 102 patients with COVID-19 who required invasive mechanical ventilation were analysed; 15 (14.7%) did not survive. Non-survivors were older (median 70 years, interquartile range [IQR] 67–75 versus median 61 years, IQR 52–66; P<0.01), and required a longer duration of ventilation (26 days, IQR 12–27 vs 8 days, IQR 5–15; P<0.01) and intensive care unit support (26 days, IQR 11–30 vs 11.5 days, IQR 7–17.3; P=0.01), with a higher incidence of acute kidney injury (15 patients [100%] vs 40 patients [46%]; P<0.01). There were 67 patients who had lung compliance data; 24 (35.8%) were classified as having high compliance and 43 (64.2%) as having low compliance. Mortality was higher in patients with high compliance (33.3% vs 11.6%; P=0.03), and was associated with a drop in compliance at day 7 (-9.3mL/cm H_2O (IQR -4.5 to -15.4) vs 0.2mL/cm H_2O (4.7 to -5.2) P=0.04).

Conclusion: COVID-19 ARDS patients with higher compliance on the day of intubation and a longitudinal decrease over time had a higher risk of death.

Ann Acad Med Singap 2021;50:686-94

Keywords: ARDS, COVID-19-associated respiratory failure, high-flow nasal cannula therapy, HFNC, post-intubation, ventilation strategies

[1] Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, Singapore
[2] Division of Respiratory and Critical Care Medicine, Department of Medicine, National University Hospital, Singapore
[3] Fast and Chronic Programmes, Alexandra Hospital, Singapore
[4] Department of Intensive Care Medicine, Ng Teng Fong General Hospital, Singapore
[5] Department of Respiratory and Critical Care Medicine, Khoo Teck Puat Hospital, Singapore
[6] Department of Intensive Care Medicine, Sengkang General Hospital, Singapore
[7] Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore
[8] Department of General Medicine, Changi General Hospital, Singapore
[9] Department of Anaesthesiology, Intensive Care and Pain Medicine, Tan Tock Seng Hospital, Singapore
[10] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[11] Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore
[12] National Centre for Infectious Diseases, Singapore
[13] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[14] Saw Swee Hock School of Public Health, National University of Singapore, Singapore
Correspondence: Prof Tsin Wen Yeo, Lee Kong Chian School of Medicine, Novena Campus, Clinical Sciences Building, 11 Mandalay Road, Level 18, Singapore 308232.
Email: yeotsinwen@ntu.edu.sg

CLINICAL IMPACT

What is New

- A portion of COVID-19 ARDS patients can present with high lung compliance following endotracheal intubation.
- This study shows that mechanically ventilated COVID-19 patients who had high initial lung compliance that subsequently decreased during their intensive care unit stay had an increased risk of mortality.

Clinical Implications

- Patients with COVID-19 ARDS may initially have high compliance, which can deteriorate over time.
- Lung ventilation strategies have to be adapted and monitored to manage COVID-19 patients with ARDS who show high initial lung compliance upon intubation.

INTRODUCTION

In December 2019, the city of Wuhan in China was the centre of a pneumonia outbreak caused by an unknown agent.[1-3] It was subsequently discovered to be a novel betacoronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[4] while the resulting clinical disease has been known as coronavirus disease 2019 (COVID-19). Since then, SARS-COV-2 has spread around the world, resulting in over 219 million cases of COVID-19 and more than 4.5 million deaths as of 20 September 2021.

It is estimated that 15–30% of hospitalised COVID-19 patients develop critical illness and require either non-invasive or invasive respiratory support.[1-3,5] The need for invasive ventilation due to acute respiratory distress syndrome (ARDS) in COVID-19 patients is associated with high mortality, with rates of up to 48–65% in reports from Wuhan.[1-3,6] High rates were similarly observed in other countries.[5,7-9] In comparison, reported mortality rates for non-COVID-19 ARDS range from 35–46%.[10] One possible explanation proposed for the higher mortality includes atypical pulmonary physiology observed in ARDS patients with COVID-19.[11] It has been reported that 70% of intubated Italian patients had preserved lung compliance, despite severe hypoxaemia.[11] This has been described as a high compliance phenotype—associated specifically with COVID-19—compared to the more familiar ARDS phenotype where compliance is low.[11,12]

Recognition of different ARDS phenotypes may have clinical relevance, since they may respond differently to the same ventilator settings, leading to different outcomes.[12,13] Heterogeneity within non-COVID-19 ARDS patients has previously been described—latent class analysis identified 2 distinct phenotypes based on inflammatory profiles in well-defined clinical cohorts.[14] However, lung compliance data were not assessed.

The differences between COVID-19 patients with high and low compliance phenotypes have not been well described within the literature, and the impact of ventilation strategy on the outcomes among the 2 groups has also not been documented. Such data is necessary for informed phenotype-specific ventilatory management.[12] In this prospective case series of intubated COVID-19 patients in Singapore, we aimed to investigate factors that affect mortality in patients with COVID-19 ARDS and the implication of lung compliance phenotypes on mortality.

METHODS

Study population

All adult patients with COVID-19 ARDS who required invasive mechanical ventilation were enrolled from 23 January to 11 May 2020, and followed up prospectively. COVID-19 diagnosis was confirmed by SARS-CoV-2 real-time polymerase chain reaction as previously described.[15] Patients were isolated and managed in the intensive care units (ICUs) of 8 public hospitals with negative pressure facilities. Collection of deidentified clinical data and waiver of written informed consent were approved by the Ministry of Health, Singapore under the Infectious Disease Act.

Data collection

We collected epidemiological data (age, sex, ethnicity, clinical symptoms and comorbidities), laboratory results on hospital admission and ICU transfer (haemoglobin, leukocyte, neutrophil, lymphocyte and platelet counts; lactate dehydrogenase, C-reactive protein, creatinine and arterial blood gas levels), fraction of inspired oxygen (FiO_2) concentration, radiological findings, ventilator mechanics (modes of ventilation, plateau pressures, positive end-expiratory pressures [PEEPs] and tidal volumes) and supportive therapy (oxygen therapy, dialysis and vasopressors) for all patients admitted to ICU. Data collection was completed on 18 May 2020 and outcomes were collated on 1 June 2020. Two researchers individually reviewed the data forms, and inconsistent or missing data were clarified with site investigators. If inconsistencies were not resolved, the patient's data were rejected and not analysed.

Definitions

We defined the date of onset of disease as the first day of symptoms reported by the patient. We defined ARDS and their severity according to the Berlin criteria,[16] and acute kidney injury in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[17]

Patients were managed using a lung protective strategy, as defined by the Acute Respiratory Distress Syndrome Clinical Network (ARDSnet) guidelines (i.e. targeting plateau pressures below 30cm H_2O by keeping tidal volume settings between 4 and 8mL/kg of predicted body weight). Driving pressure was defined as the difference between plateau pressure and PEEP. Plateau pressures were acquired by performing an end-inspiratory breath hold manoeuvre, with the patient either on neuromuscular blockers or deep sedation to prevent spontaneous respiration. This was done within the first 12 hours of ventilation and was repeated based on the discretion of the treating physician.

High compliance phenotype was defined as a static compliance of <40mL/cm H_2O while low compliance was defined as a static compliance of <40mL/cm H_2O as previously described.[13,18] In this study, static compliance was calculated using exhaled tidal volumes divided by the driving pressure.

Statistical analysis

The group characteristics, respiratory physiological parameters, and outcomes in all patients were analysed. The difference in outcomes between the high and low compliance phenotypes were evaluated. Continuous variables were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]) depending on distribution, and categorical variables were expressed as frequency and percentage. We compared differences for continuous variables using two-sample t-test or Wilcoxon rank-sum test depending on the distribution, and chi-square test or Fisher's exact test for categorical variables. Logistic regression was used to adjust for factors associated with death and the high and low compliance phenotype. We used an agnostic approach to determine the covariates included in the model, performing forward variable selection with the likelihood ratio test to add covariates one at a time. At each variable selection step, the most significant covariate that was not in the current model was added if its *P* value was <0.05. No further covariates were added if the remaining covariates had *P* values >0.05. Tests were two-sided with significance level set at <0.05. Analyses were performed using MedCalc statistical software version 19.1.7 (MedCalc Software Ltd, Ostend, Belgium) and STATA version 13.1 (StataCorp, College Station, US).

RESULTS

Baseline characteristics

There were 102 patients with confirmed COVID-19 who required invasive ventilation in the ICU between 23 January and 11 May 2020. The median age was 62 years (IQR 54–68), 75 (73.5%) were male and the median body mass index was 26 (IQR 23.3–30.5). There were 64 (62.8%) patients with hypertension, 52 (51%) with hyperlipidaemia, 38 (37.3%) with diabetes mellitus and 17 (16.7%) with ischaemic heart disease. A total of 15 (14.7%) patients had a fatal outcome. There was no difference in baseline demographics, comorbidities and baseline lab investigations between survivors and non-survivors (Table 1).

Table 1. Patient demographics, comorbidities and lab investigations

	Total patients (N=102)	Survivors (n=87)	Non-survivors (n=15)	*P* value
Demographics				
Age, median (IQR), years	62 (54–68)	61 (53–66)	70 (64–75)	<0.01
Male, no. (%)	75 (73.5)	62 (71.3)	13 (86.7)	0.34
BMI, median (IQR), kg/m^2	26 (23.2–30.6)	26 (23.4–30.7)	26.3 (22.7–28)	0.29
Race, no. (%)				
Chinese	62 (60.8)	54 (62.1)	8 (53.3)	0.52
Malay	17 (16.7)	16 (18.4)	1 (6.7)	0.46
Indian	10 (9.8)	7 (8.0)	3 (20)	0.16
Others	13 (12.7)	10 (11.5)	3 (20)	0.40

Table 1. Patient demographics, comorbidities and lab investigations (Cont'd)

	Total patients (N=102)	Survivors (n=87)	Non-survivors (n=15)	*P* value
Comorbidities, no. (%)				
Hypertension	64 (62.7)	55 (63.2)	9 (60)	0.81
Diabetes mellitus	38 (37.3)	32 (36.8)	6 (40)	0.81
Hyperlipidaemia	52 (51)	45 (51.7)	7 (46.7)	0.72
Ischaemic heart disease	17 (16.7)	12 (13.8)	5 (33.3)	0.13
Cerebrovascular accident	5 (4.9)	5 (5.7)	0	1.00
Congestive cardiac failure	4 (3.9)	4 (4.5)	0	1.00
Cancer	8 (7.8)	6 (6.9)	2 (13.3)	0.33
Chronic obstructive pulmonary disease	3 (2.9)	3 (3.4)	0	1.00
Asthma	4 (3.9)	3 (3.4)	1 (6.7)	0.48
Severity scores, median (IQR)				
APACHE II	14 (10–22)	14 (10–22)	13.5 (10.8–20.3)	0.93
SOFA	4 (2–7)	4 (2–8)	3 (2.8–4.3)	0.01
Lab investigations, median (IQR)				
White cells, $x10^9$/L	7.8 (5.6–10.2)	8.1 (6.1–10.1)	5.7 (3.4–12.7)	0.47
Neutrophils, $x10^9$/L	6.2 (3.9–8.5)	6.6 (4.3–8.5)	4.2 (2.7–10.2)	0.09
Lymphocytes, $x10^9$/L	0.78 (0.57–1.14)	0.79 (0.59–1.2)	0.61 (0.5–0.9)	0.07
Haemoglobin, mg/dL	13.3 (12.1–14.2)	13.1 (12–14.1)	13.5 (12.6–14.6)	0.34
Platelets, $x10^9$/L	223 (161–288)	223 (164–291)	203 (128–259)	0.41
C-reactive protein, mg/dL	140.8 (81.9–192)	141 (81.6–198.3)	129 (91.1–161)	0.74
Procalcitonin, µg/L	0.31 (0.13–0.69)	0.31 (0.13–0.71)	0.29 (0.11–0.44)	0.47
Creatinine, µmol/L	82 (64–100)	79.5 (62.5–100)	91 (72–107)	0.34
Lactate dehydrogenase, U/L	675 (449–919)	658 (433–891)	721 (517–1161)	0.22
Albumin, g/L	33 (30–36)	33 (30–36)	33 (30–35)	0.34
Alanine transaminase, U/L	39 (24–60)	40 (24–83)	36 (25–44)	0.41
Aspartate aminotransferase, U/L	51 (38–74)	50.5 (37.5–81.3)	55.5 (34–67.5)	0.50
Alkaline phosphatase, U/L	84 (59–108)	85 (61–118)	61 (55–90)	0.12
Outcomes, no. (%)				
Shock	59 (57.8)	52 (59.8)	7 (46.7)	0.34
Cardiac event[a]	23 (22.5)	17 (19.5)	6 (40)	0.08
Ventilator associated pneumonia	36 (35.3)	27 (31)	9 (60)	0.03
Pneumothorax	5 (4.9)	5 (5.7)	0	1.00
Extracorporeal membrane oxygenation	5 (4.9)	3 (3.4)	2 (13.3)	0.24
Acute kidney injury	55 (53.9)	40 (46.0)	15 (100)	<0.01
Dialysis	30 (29.4)	16 (20.3)	14 (93.3)	<0.01

APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: body mass index; IQR: interquartile range; SOFA: sequential organ failure score
[a] Non-ST-elevated myocardial infarction, type 2 myocardial infarction or atrial fibrillation

Table 2. Oxygen requirements prior to intubation, patients' severity of ARDS, lung ventilation mechanics and mortality outcomes of patients with compliance data

	Total (N=67)	High compliance (n=24)	Low compliance (n=43)	*P* value
Oxygen delivery prior to intubation				
Nasal cannula, no. (%)	10 (15.2)	5 (20.8)	5 (11.6)	0.48
Venturi mask, no. (%)	19 (28.8)	8 (33.3)	11 (25.5)	0.54
Non-rebreather mask, no. (%)	20 (30.3)	6 (25)	14 (32.5)	0.48
High-flow nasal cannula, no. (%)	22 (32.8)	6 (25)	16 (37.2)	0.31
PaO_2/FiO_2 prior to intubation[a]	128 (85–170)	145 (112–183)	112 (76–161)	0.05
PaO_2/FiO_2 after intubation[a]	175 (138–223)	166 (137–226)	176 (138–220)	0.53
Patients' severity of ARDS, no. (%)				
Mild ARDS	23 (34.3)	10 (41.7)	13 (30.2)	0.35
Moderate ARDS	36 (53.7)	13 (54.2)	23 (53.5)	0.96
Severe ARDS	8 (11.9)	1 (4.2)	7 (16.3)	0.24
Lung ventilation mechanics				
Positive end-expiratory pressure, cm H_2O[a]	12 (10–14)	12 (10–13.5)	10 (10–14)	0.94
Tidal volume, mL/kg[a]	6.4 (6–7)	6.5 (6–7.3)	6.3 (5.9–6.9)	0.53
Plateau pressure, cm H_2O[a]	24 (20–26)	20 (18–22)	25 (23–28)	<0.01
Driving pressure, cm H_2O[a]	11 (9–14)	8 (8–10)	13 (12–15)	<0.01
Compliance, mL/cm H_2O[a]	35 (28.5–46.8)	50 (46–55.9)	30 (25.1–34.6)	<0.01
Days on ventilator[a]	12 (6–22)	12 (6–27)	11 (5–17)	0.32
Prone, no. (%)[b]	38 (57.6)	16 (66.7)	22 (52.4)	0.26
Neuromuscular blockade, no. (%)[c]	50 (75.8)	19 (79.2)	31 (73.8)	0.63
Tracheostomy, no. (%)	10 (14.9)	3 (12.5)	7 (16.3)	1.00
Non-survivors, no. (%)	13 (19.4)	8 (33.3)	5 (11.6)	0.03

ARDS: acute respiratory distress syndrome
[a] Values expressed as median (interquartile range)
[b] Received prone ventilation to manage respiratory failure
[c] Received neuromuscular blockade agents to manage respiratory failure

Non-respiratory complications

A large proportion of patients developed organ dysfunction with 55 (53.9%) diagnosed with acute kidney injury; renal replacement therapy was required in 30 (29.4%) patients (Table 1). A total of 23 (22.5%) patients had cardiac complications during the ICU stay, 6 (5.8%) diagnosed with non-ST elevation acute myocardial infarction, 5 (4.9%) with type 2 myocardial infarction and the remaining 12 (11.7%) with probable myocarditis. Echocardiograms were done for 24 patients with no significant abnormality detected except for right ventricular wall motion abnormalities in 1 patient. There were 12 (11.7%) patients with shock requiring multiple inotropes, while 47 (46%) required short-term inotrope use mainly around the time of intubation. The incidence of confirmed thrombotic events was low; 2 (1.9%) patients were diagnosed with ischaemic cerebrovascular accidents, 2 (1.9%) with deep venous thrombosis and none with pulmonary embolism, with 10 computed tomography (CT) pulmonary angiograms done to exclude the diagnosis.

Lung compliance

Lung compliance data were available for 67 patients; 24 (35.8%) were classified as having a high compliance phenotype and 43 (64.2%) as having a low compliance phenotype. Among the total of 102 patients with confirmed COVID-19 who required invasive ventilation in the ICU, 21 were excluded because no lung compliance data was available. Nine patients did not

meet ARDS criteria post-intubation, and the PaO_2/FiO_2 (PF) ratio was not assessed after intubation in 5 patients, who were also excluded from the analysis.

Patients with high compliance were significantly older than those in the lower compliance group (median 67 years [IQR 59–71] vs median 58 years [IQR 51–64]; $P<0.01$), but there were no other significant differences with regards to demographics, symptoms, days from the development of clinical symptoms to intubation and laboratory results between the 2 groups (Supplementary Online Table 1).

After intubation, the median PF ratio between the 2 groups were not significantly different (low compliance: 166 [IQR 137–226] vs high compliance: 176 [IQR 138–220]; $P=0.53$), but plateau and driving pressures were higher in patients with low compliance (Table 2). Lung compliance data were available on day 7 after intubation for 29 patients, allowing assessment of longitudinal changes. Patients who were classified as having low compliance had no significant change at day 7 (1.8mL/cm H_2O [IQR -4.9 to 3.1], n=17). However, there was a significant reduction for patients initially classified as having high compliance (-10.5mL/cm H_2O, [IQR -4.9 to -18.15], n=12; $P=0.01$) (Fig. 1).

Outcomes

There were 87 patients who were extubated and discharged from the ICU, and 15 (14.7%) had a fatal outcome. Non-survivors were older (median 70 years, IQR 67–75 vs median 61 years, IQR 52–66; $P<0.01$), stayed on the ventilator longer (26 days, IQR 12–27 vs 8 days, IQR 5–15; $P<0.01$), stayed in the ICU longer (26 days, IQR 11–30 vs 11.5 days, IQR 7–17.3; $P=0.01$) and a higher proportion had acute kidney injury (15 patients [100%] vs 40 [46%]; $P<0.01$). Non-survivors received high-flow nasal oxygen before intubation (8 patients [53.5%] vs 16 [18.6%]; $P=0.01$), prone ventilation (15 [100%] vs 38 [43.7%]; $P<0.01$), neuromuscular blockers (15 [100%] vs 55 [63.2%]; $P=0.01$), and required dialysis (14 [93.3%] vs 16 [20.3%]; $P<0.01$) (Table 3). Non-survivors also had a significant decrease in compliance (n=8, -9.3mL/cm H_2O, IQR -4.5 to -15.4) between the day of intubation and day 7 of post-intubation, compared with survivors (n=21, 0.2mL/cm H_2O, IQR 4.7 to -5.2; $P=0.04$) (Fig. 1).

Mortality was significantly higher in patients who were initially in the higher compliance group compared to the those classified as low compliance (33.3% vs 11.6%; $P=0.03$) (Table 3). Using logistic regression to adjust for age, use of high-flow nasal oxygen and acute kidney injury, the effect on mortality remained significant (odds ratio [OR] 3.5, 95% confidence interval [CI] 1.1–12; $P=0.04$). Within the high compliance group, mortality was higher in the subgroup that switched from having high to low compliance (5/7 patients, 57.1%) compared with those that did not (1/5, 20%) but this was not statistically significant ($P=0.1$). Other outcomes were not significant between the groups (Supplementary Online Table 2).

DISCUSSION

In our prospective study of 102 mechanically ventilated patients with COVID-19, we found that mortality was associated with older age, high-flow nasal cannula (HFNC) use, and development of acute kidney injury requiring dialysis. Among patients with lung compliance results post-intubation, mortality was significantly higher in those initially classified as having high compliance compared with low compliance. Among patients with high compliance initially, mortality was associated with a significant decrease in lung compliance in the first week after intubation.

It has been proposed that COVID-19 patients are more likely to present with an "atypical" form of ARDS characterised by severe hypoxaemia with relatively preserved lung compliance and low elastance, termed the L phenotype.[11-13,19,20] This is in contrast to the H phenotype, which describes ARDS with low compliance and high elastance, the phenotype more familiar to intensivists.[21] Distinguishing the ARDS phenotype is important because the 2 phenotypes are predicted to respond differently to alveolar recruitment strategies and high PEEP. In those with preserved compliance, these interventions risk worsening lung injury through overdistention.[13]

Calfee et al. used latent class analysis to identify 2 ARDS phenotypes based on inflammatory markers. They found that recruitment manoeuvres and PEEP were associated with reduced mortality in patients with a hyperinflammatory profile (termed phenotype 2), whereas these manoeuvres increased mortality in those with a less inflammatory phenotype type 1.[14] More recently, Constantin et al. have shown that ARDS patients can be broadly classified into focal or non-focal ARDS. They reported mortality improvement in those with non-focal ARDS if lower tidal volumes and higher PEEP were used. In contrast, mortality was lower in those with focal ARDS if higher tidal volumes and lower PEEP were used. Equally important, they found that the misclassification resulted in an increased mortality.[22] It is possible that the clinical response of patients starting with higher compliance is similar to the less hyperinflammatory phenotype 1 as described by Calfee et al., and focal ARDS described by Constantin et al., whereas patients with lower compliance is similar

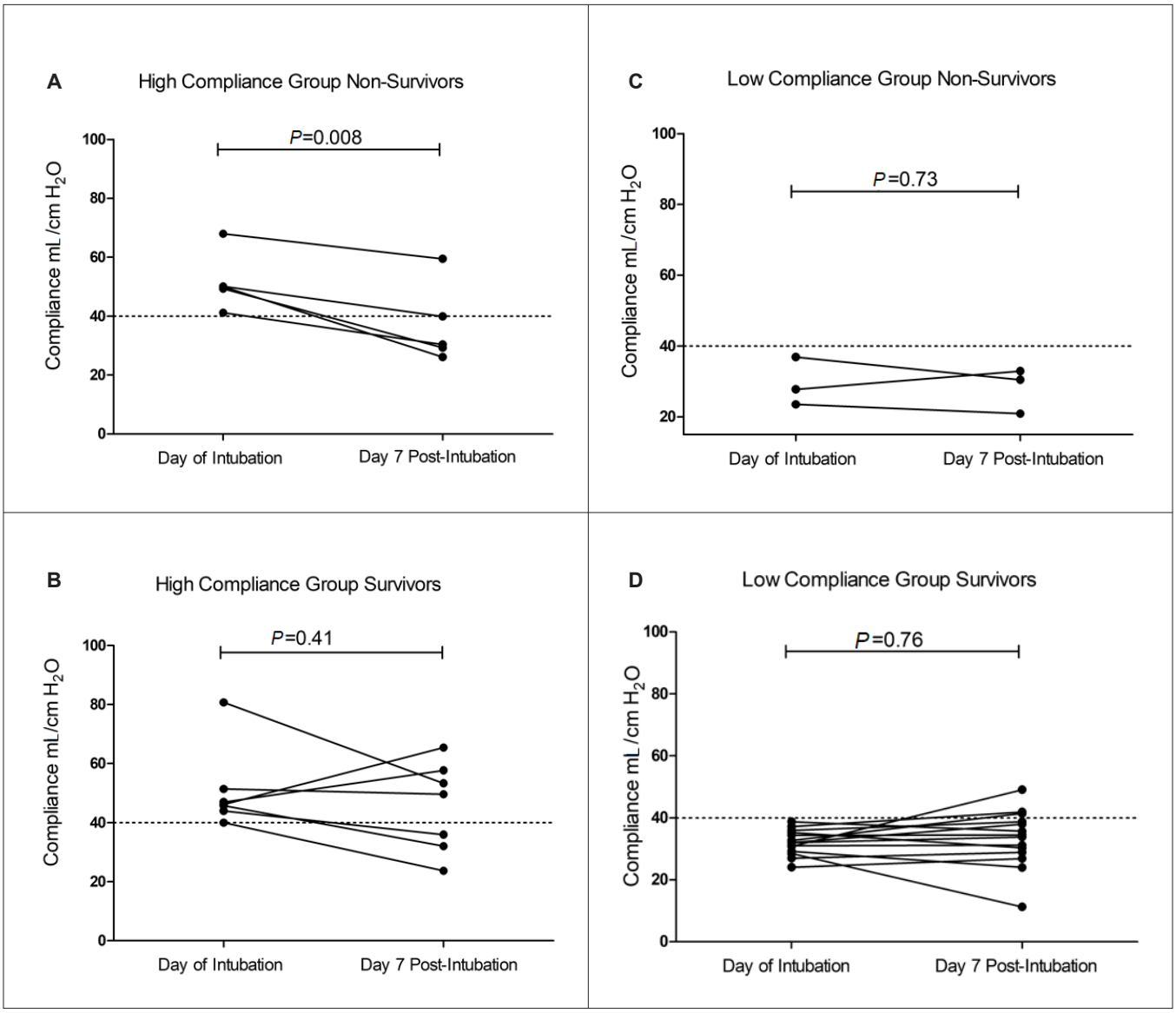


Fig. 1. Lung compliance on the day of intubation and 7 days post-intubation. (A) Patients with high compliance following intubation with a fatal outcome. (B) Patients with high compliance following intubation who survived. (C) Patients with low compliance following intubation with a fatal outcome. (D) Patients with low compliance following intubation who survived.

to inflammatory phenotype 2 and non-focal ARDS. However, C-reactive protein and procalcitonin levels were not significantly different between the groups, although other markers may be more sensitive in the evaluation of inflammation and cytokine release syndrome.

Critically ill COVID-19 patients have an increased risk of cardiac complications and thrombosis. The proportion of patients in the study with cardiac complications appears similar to previous reports.[3,23] More than half had non-specific elevation in troponin levels with normal electrocardiograms, while the remainder had no evidence of myocardial ischaemia. However, echocardiography done on these patients were normal, except for reduced left ventricular contractility in one patient. Incidences of confirmed ischaemic cerebrovascular accidents, deep venous thrombosis and pulmonary embolism were low in the study.

The mortality rate in the current study was 14.7%, which is lower than that reported among COVID-19 patients with ARDS in Wuhan, where mortality rates ranged from 50 to 65%.[1-3,6] Mortality rates have also been reported in the US, with studies from Seattle and New York reporting rates of 50–70%.[5,9,24] Although the mortality rates reported from northern Italy and the UK are lower, they are still close to twice the mortality we observed at 28% and 37%, respectively.[7,8] Interestingly,

Table 3. Oxygen delivery and lung ventilation mechanics for patients who survived and did not survive

	Total patients (N=102)	Survivors (n=87)	Non-survivors (n=15)	*P* value
Oxygen delivery prior to intubation				
Nasal cannula, no. (%)	17 (16.7)	14 (16.3)	3 (20)	0.71
Venturi mask, no. (%)	34 (33.3)	29 (33.7)	5 (33.3)	1.00
Non-rebreather mask, no. (%)	32 (31.4)	31 (36.0)	1 (6.7)	0.03
High-flow nasal cannula, no. (%)	24 (23.5)	16 (18.6)	8 (53.3)	0.01
PaO_2/FiO_2 prior to intubation[a]	126 (87–174)	126 (90–176)	122 (83–169)	0.83
PaO_2/FiO_2 after intubation[a]	183 (135–244)	188 (140–256)	155 (116–189)	0.07
Lung ventilation mechanics				
Positive end expiratory pressure, cm H_2O[a]	10 (10–12)	10 (10–13)	10 (8–12)	0.54
Plateau pressure, cm H_2O[a]	23 (20–26)	24 (20–27)	22 (19–23)	0.17
Driving pressure, cm H_2O[a]	12 (9–14)	12 (9–15)	10.5 (8–13.3)	0.29
Compliance, mL/cm H_2O[a]	35.3 (29–47)	34.5 (29.1–43.9)	46.8 (27.9–53.1)	0.17
Days on ventilator[a]	10 (5–17.3)	8 (5–15)	26 (12–27)	<0.01
Days in ICU[a]	13 (7–20)	11.5 (7–17.3)	26 (11–30)	0.01
Prone, no. (%)[b]	53 (52)	38 (43.7)	15 (100)	<0.01
Neuromuscular blockade, no. (%)[c]	70 (68.6)	55 (63.2)	15 (100)	0.01

ICU: intensive care unit
[a] Values expressed as median (interquartile range)
[b] Received prone ventilation to manage respiratory failure
[c] Received neuromuscular blockade agents to manage respiratory failure

a study from Boston, US reported a mortality rate of 16.7%, and also a preponderance of lower over higher compliance.[25]

In Singapore, there has been increased use of HFNC therapy for COVID-19-associated respiratory failure, coupled with awake prone ventilation that has been reported to improve oxygenation.[26] However, in our study, use of HFNC was associated with increased mortality. Patients may be taking large-volume breaths resulting in patient self-inflicted lung injury, although there was no difference in compliance post-intubation between those who received HFNC and those that did not. A PF ratio of <200 has been associated with HFNC failure and the need for invasive ventilation, which may also explain the poorer outcomes in this group.[27] More studies are needed to understand the optimal usage of HFNC in COVID-19 patients.

Our study had several limitations. Firstly, although ventilator strategies were similar across institutions, the mode of ventilation and management were left to the discretion of the treating physician. Secondly, day 7 compliance data were not available for more than half the patients because most patients were already extubated or undergoing weaning from the ventilator, preventing measurement of plateau pressure. Thirdly, the evolving therapeutic landscape in COVID-19 meant that the majority of critically ill patients received a variety of antiviral therapies, and the effects of these on our ICU outcomes cannot be assessed.

CONCLUSION

In summary, mortality in mechanically ventilated COVID-19 patients was higher in patients who were older, had acute kidney injury and/or placed on dialysis, and had higher lung compliance at intubation that was associated with decreasing compliance over time.

REFERENCES

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507-13.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497-506.

3. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
4. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-33.
5. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323:2052-9.
6. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
7. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected with SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020; 323:1574-81.
8. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.
9. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020;382:2012-22.
10. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016; 315:788-800.
11. Gattinoni L, Coppola S, Cressoni M, et al. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2020;201:1299-300.
12. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. JAMA 2020;323:2329-30.
13. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46:1099-102.
14. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2014;2:611-20.
15. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA 2020;323:1488-94.
16. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
17. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138.
18. Bos LDJ, Paulus F, Vlaar APJ, et al. Subphenotyping Acute Respiratory Distress Syndrome in Patients with COVID-19: Consequences for Ventilator Management. Ann Am Thorac Soc 2020;17:1161-3.
19. Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med 2020;8:1201-8.
20. Osuchowski MF, Winkler MS, Skirecki T, et al. The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity. Lancet Respir Med 2021;9:622-42.
21. Panwar R, Madotto F, Laffey JG, et al. Compliance Phenotypes in Early Acute Respiratory Distress Syndrome before the COVID-19 Pandemic. Am J Respir Crit Care Med 2020;202:1244-52.
22. Constantin JM, Jabaudon M, Lefrant JY, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. Lancet Respir Med 2019;7:870-80.
23. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
24. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA 2020;323:1612-4.
25. Ziehr DR, Alladina J, Petri CR, et al. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. Am J Respir Crit Care Med 2020;201:1560-4.
26. Ng Z, Tay WC, Ho CHB. Awake Prone Positioning for Non-intubated Oxygen Dependent COVID-19 Pneumonia Patients. Eur Respir J 2020;56:2001198.
27. Wang K, Zhao W, Li J, et al. The experience of high-flow nasal cannula in hospitalized patients with 2019 novel coronavirus-infected pneumonia in two hospitals of Chongqing, China. Ann Intensive Care 2020;10:37.

ORIGINAL ARTICLE

Ann Acad Med Singap 2021;50:695-702
https://doi.org/10.47102/annals-acadmedsg.2021134

Parental perception and guideline awareness of children's lifestyle behaviours at ages 5 to 14 in Singapore

Phaik Ling Quah [1]*PhD*, Benny Kai Guo Loo [2]*MBBS (S'pore)*, Nurul Syaza Razali [1]*BSc*, Nurul Sakinah Razali [1]*BSc*, Chin Chye Teo [1]*PhD*, Kok Hian Tan [1,3]*MBBS (S'pore)*

ABSTRACT

Introduction: There are limited data on the descriptive lifestyle behaviour of school-age children in Singapore.

Methods: A total of 100 parents of children ages 5 to 14 participated in a parents' proxy-reported survey. Frequency of moderate physical activity (PA) and vigorous PA was assessed, while t-tests or chi-square test was used to examine differences between weekdays and weekends for sleep, screen viewing time (SVT) and sedentary behaviour (SB).

Results: Of the 100 children (68% of Chinese ethnicity, 59% boys, mean age 9.1±2.9 years), 31% were overweight or obese, with body mass index z-score of >1. For moderate and vigorous PA participation in a typical week, 32.0% and 43.0%, respectively, did not participate, while median (interquartile range) days of participation were 3 (2–3) days/week and 2 (1–3) days/week for a duration of 60 (interquartile range 30–120) minutes/session. When comparing weekends with weekdays, the means (standard deviation) of both SVT and sleep duration were higher on weekends (SVT: 4.1 [2.9] versus 3.3 [3.1] hours/day, P=0.07; sleep: 8.8 [1.5] vs 8.3 [1.3] hours/day, P=0.02), while there were no significant differences for SB. A higher proportion of children had SB of ≥10 hours/day and slept <8 hours/day on weekdays compared with on weekends (SB: 23.5% vs 20.6%, P>0.05; sleep:18.8% vs 2.1%, P<0.05), while the proportion exceeding SVT of 2 hours/day were higher on weekends than on weekdays (63.8% vs 45.4%, P=0.03). Overall, there was higher parental awareness of sleep guidelines (80.0%), but lower awareness of PA (51.0%) and SVT (59.0%) guidelines.

Conclusion: Lifestyle behaviours were suboptimal in Singapore children compared with existing overseas guidelines, indicating a need for an integrated guideline with greater dissemination.

Ann Acad Med Singap 2021;50:695-702

Keywords: Childhood and adolescents, integrated guideline, lifestyle behaviours, physical activity, screen viewing time, sleep

INTRODUCTION

Evidence from longitudinal studies in Singapore has suggested that long-term health implications on children stems from less-than-optimal lifestyle behaviours,[1-3] encompassing physical activity (PA),[4] sleep[5] and sedentary behaviour (SB) which includes screen viewing time (SVT).[6]

In recent years, specific combinations of integrated movement behaviours (i.e. sufficient PA, low SB, limited SVT and adequate sleep) known as the 24-hour movement guidelines for children 5–17 years were developed in Canada[7] and Australia.[8] The greater the number of integrated guidelines accomplished, the better the health-related quality of life.[9] These behaviours have also been independently associated with desirable health indicators related to cardiometabolic health[4,5,10] and better psychosocial health.[5,11] The recommendations from these guidelines include sufficient PA (e.g. moderate to vigorous PA of ≥60 min/day), limited SVT (≤2 hours/day) and adequate sleep duration (e.g. 9–11 hours/night for children aged 5–13 years).[7,8] Data of children aged 5.5 years from the Growing Up in Singapore Towards Healthy Outcomes birth cohort study has shown that relatively few children (5.5%)[12] adhered to these guidelines.[7,13] The study further

[1] Division of Obstetrics and Gynaecology, KK Women's and Children's Hospital, Singapore
[2] General Paediatric Service, KK Women's and Children's Hospital, Singapore
[3] Duke-NUS Medical School, Singapore
Correspondence: Prof Kok Hian Tan, Maternal Fetal Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899.
Email: tan.kok.hian@singhealth.com.sg

CLINICAL IMPACT

What is New

- This study highlights the suboptimal lifestyle behaviours of the Singaporean children aged 5–14 years.
- Findings also point to the lack of awareness of existing activity guidelines among parents with children in this age group.

Clinical Implications

- This study led to the development of the Singapore Integrated 24-Hour Activity Guidelines for Children And Adolescents to help with better monitoring and improvement of these behaviours.

suggested the adaption of the integrated movement guidelines for Singapore to better monitor children's daily activities to achieve the desirable health indicators. However, more data on lifestyle behaviours are first required in children from older age groups to support the development of such guidelines.

Currently, most of the data we have on lifestyle behaviours of children in Singapore come from those of preschooler age (3–6 years)[1,3,12,14-16] or younger (below 2 years).[2,17] Cross-sectional data in the preschooler age group have shown that time spent engaged in moderate to vigorous PA is low, while time spent in SB is high;[15] the duration of night-time sleep is significantly lower than recommended values.[16] At ages 2–3 years, 50% of children were already spending >2 hours/day on SVT, exceeding the recommended guidelines for this age group.[14] Studies in children of ages 5 years and above from Singapore spanning across the school-going age groups (kindergarten, primary and secondary school) are not as comprehensive, especially on evidence surrounding SVT, SB and sleep. Existing studies have focused on either the younger age group only (primary school at ages 7–12)—with only one study on PA[18]—and the adolescent age group only (secondary school at ages 13–18 years), examining PA[19] and sleep.[20]

In view of the limited data in children aged 5 years and older, our study aimed to comprehensively assess the lifestyle behaviours of Singapore children aged 5–14 years. Specifically, this survey aimed to (1) describe PA, SVT, SB and sleep; (2) compare SVT, SB and sleep between weekdays and weekends; and (3) describe the parental perceptions of child health and awareness of existing guidelines.

METHODS

Study sample

A convenience sampling method was used to recruit participants from the KK Women's and Children's Hospital for this survey. Eligible participants had to be Singaporean or permanent resident parents (mother or father) of children aged 5–14 years, who were able to read and understand English. Parents would need to give verbal consent for an anonymous survey before they were given either a hard copy of the survey to complete or an electronic version via FormSG (https://form.gov.sg/). Parents who completed the survey received SGD25 in cash, and 100 parents completed this survey within a 1-month period from 1 October to 1 November 2020. The research procedures in this study received formal approval for an exempt review by the SingHealth Centralised Institutional Review Board.

Data collection

The survey comprised 33 items that collected data on demographics, PA, SB, SVT, sleep habits (night-time sleep and day-time napping), parental perceptions on child's health and well-being, and parental awareness of lifestyle guidelines for children and adolescents. The parents would self-report their demographic characteristics and report their child's demographics and lifestyle behaviours by proxy. They were asked to recall their child's past 7-day lifestyle and activities while completing the survey questions. Items on PA and SB were adapted from the International Physical Activity Questionnaire,[21] while the items on sleep were adapted from the Child Sleep Habits Questionnaire;[22] both questionnaires have been widely used to assess PA or sleep.[23] Recreational SVT was captured as the average time a child spends on a screen.[14] The entire survey took parents approximately 10–15 minutes to complete.

Assessment of physical activity and sedentary behaviour

Examples of activities common in children were stated as a guide for parents alongside questions on PA levels: vigorous (i.e. fast running, fast swimming, or fast cycling), moderate (i.e. fast walking or regular-paced cycling) and light (i.e. recreational or leisure walking). Parents reported by proxy their child's SB separately for weekdays and weekends, with SB being defined as time spent at school and at home, including time spent sitting at a desk studying and reading, as well as reclining, sitting or lying down to watch television.[24]

Assessment of screen time

Screen viewing time duration (in hours and minutes) was assessed using the questions "In a typical week, how much time does your child spend on recreational screen viewing time on a weekday?" and "In a typical week, how much time does your child spend on recreational screen viewing time on a weekend?" Screen time included the use of 3 types of screen devices: television (viewing or playing television games), computer and handheld devices.

Assessment of sleep

Parents reported their child's bedtime, waketime, naptime duration (in hours and minutes) and naptime frequency separately for weekdays and weekends. Bedtimes and waketimes were used to calculate total 24-hour sleep times for each child. Naptime frequency was captured with the question "In the past week, how many naps does your child take per day?", with the response options of "No naps", "1 nap", "2 naps" and "3 naps or more". Naptime duration was captured with the questions "What is the average time spent on a nap during a weekday?" and "What is the average time spent on a nap during a weekend?".

Parental perception of child' health

Parental perception of their child's weight, calorie intake, PA, screen time exposure and sleep were assessed with the question "Do you think your child is …", with the response options of "Overweight", "Normal weight" and "Underweight". The other 4 questions were (1) "Do you feel that your child receives adequate amount of physical activity to benefit his/her growth, development and health?"; (2) "Are you concerned about the amount of recreational screen time your child is currently exposed to?"; (3) "Do you think your child is getting adequate sleep to support his/her growth, development and health?", with the response options of "Yes" and "No"; and (4) "Do you think your child is receiving adequate calories to support his/her growth, development and health?", with the response options of "Yes", "Too much" and "No".

Parental awareness of lifestyle guidelines for children

To assess parental awareness of available lifestyle guidelines for children, parents were asked 3 separate questions regarding PA, sleep and screen time: "Are you aware of the current recommendations regarding the amount of physical activity/sleep/screen time your child should be receiving per day?", with the response options of "Yes" and "No".

Statistical analyses

Continuous datasets that were normally distributed were presented as mean and standard deviation (SD), while non-normally distributed datasets were presented as median and interquartile range (IQR). SVT, SB and sleep were analysed as continuous variables and categorical variables. SVT was categorised into 3 levels (≤2, >2–4 and >4 hours), as evidence has shown that recreational SVT of more than 2 hours daily is associated with the most adverse health outcomes.[7,11,25] SB was categorised into <10 and ≥10 hours, based on reported evidence that SB taking up more than 60–70% of one's waking day is considered high SB.[26] In this survey, 10 hours of SB out of 15 waking hours (considering mean duration of 9 hours of sleep) is about 67% of a child's day. Sleep was categorised into 3 levels (<8, 8–9 and >9 hours) based on the recommended amount of sleep for school-aged children of 7–18 years (i.e. 8–9 hours/day).[27] The independent t-test and the chi-square test were used to compare continuous and categorical variables, respectively, between the weekday and weekend. Sex- and age-specific body mass index (BMI) z-scores were derived using the World Health Organization (WHO) references.[28] The cut-offs for overweight and obese were defined as +1SD and +2SD, respectively, above the reference distribution as per WHO recommendations.[29] Statistically significant results were determined at 2-sided $P<0.05$. All analyses were performed using the STATA software version 13 (StataCorp, College Station, US).

RESULTS

Study participants

Parent and child characteristics are detailed in Table 1. The mean age of the 100 respondents was 40.5±4.8 years, with the majority being mothers (89.0%). Of all the parents, 68.0% were Chinese, 62.6% had a university education and 63.0% were reporting by proxy for their first child.

Child demographics revealed that 50.9% were boys, the mean age was 9.1±2.9 years, and 92.0% did not have any chronic illnesses. The mean BMI z-score was -0.22±2.27; 18.0% of the children were overweight with a BMI z-score of >1, and 13% were obese with a BMI z-score of >2.

Parents' proxy-reported physical activity

Table 2 shows the descriptive characteristics of parents' proxy-reported child engagement in PA. In a typical week, 57.0%, 68.0% and 92.0% of children participated

Table 1. Characteristics of the parent respondents of the survey and their children (N=100)

Characteristics	No. (%) or mean ± standard deviation
Respondent characteristics	
Parent	
Mother	89 (89.0)
Father	11 (11.0)
Age, year	40.5±4.8
Ethnicity	
Chinese	68 (68.0)
Malay	25 (25.0)
Indian	7 (7.0)
Education[a]	
University	62 (62.6)
Secondary	31 (31.3)
Primary	6 (6.1)
Child characteristics	
Birth order	
First-born	63 (63.0)
Second-born or later-born	37 (37.0)
Sex	
Male	59 (59.0)
Female	41 (41.0)
Chronic illness[b]	
No	92 (92.0)
Yes	8 (8.0)
Age (year)	9.1±2.9
Body mass index (z-scores)[c]	-0.22±2.27
Overweight (>+1 z-score)[c]	18 (18.0)
Obese (>+2 z-score)[c]	13 (13.0)

[a] Missing data, n=1
[b] Chronic illness includes asthma, diabetes, congenital heart disease, cerebral palsy, sickle cell anaemia, spina bifida and epilepsy
[c] Sex- and age-specific body mass index z-scores were derived using the World Health Organization references

in vigorous PA, moderate PA and low PA, respectively. Median days of children participating in vigorous PA and moderate PA in a typical week were 3 (IQR 2–3) days/week and 2 (IQR 1–3) days/week for a duration of 60 (IQR 30–120) minutes/session, respectively. The median frequency of low PA engagement was 5 (IQR 3–7) days/week for 30 (IQR 20–60) minutes/session.

Table 2. Parents' proxy-reported engagement in physical activity, frequency per week and duration per session of vigorous, moderate and light physical activity in children aged 5–14 years

Physical activity	No. (%) or median (IQR)
Vigorous	
Yes	57 (57.0)
Frequency per week (day)	3 (2–3)
Duration per session (min)	60 (30–120)
No	43 (43.0)
Moderate	
Yes	68 (68.0)
Frequency per week (day)	2 (1–3)
Duration per session (min)	60 (30–120)
No	32 (32.0)
Light	
Yes	92 (92.0)
Frequency per week (day)	5 (3–7)
Duration per session (min)	30 (20–60)
No	8 (8.0)

IQR: interquartile range

Parents' proxy-reported SVT, SB and sleep

Table 3 shows the SVT, SB and sleep duration assessed in the children, comparing weekdays with weekends. Most children were engaged in SVT on weekdays (90%) and weekends (94%), and the children had, on average, higher SVT on weekends than on weekdays (4.1±2.9 vs 3.3±3.1 hours/day; P=0.07). Similarly, the percentage of children exceeding 2 hours/day of SVT (i.e. >2–4 and >4 hours/day) tended to be higher on weekends (29.8% and 34.0%, respectively) than on weekdays (25.6% and 19.8%, respectively; P=0.03). In contrast, the overall average time spent in SB was higher on weekdays than on weekends (6.5±3.3 vs 6.0±3.1 hours/day, P=0.26), with a higher percentage of children spending more time in high SB (≥10 hours/day) on weekdays than on weekends (23.5% vs 20.6%, P=0.23). Children in this survey had less night-time sleep on weekdays than on weekends (8.3±1.3 vs 8.8±1.5 hours/day, P=0.02), with 18.8% of children receiving less than 8 hours of sleep on weekdays compared with only 2.1% of children on weekends (P=0.001).

Table 3. Parents' proxy-reported screen viewing time, sedentary behaviour and sleep in children aged 5–14 years[a]

	Weekday	Weekend	*P* value
Screen time, hour/day[b]			
≤2	47 (54.6)	34 (36.2)	
>2–4	22 (25.6)	28 (29.8)	
>4	17 (19.8)	32 (34.0)	
Mean±SD	3.3±3.1	4.1±2.9	0.07
Sedentary behaviour, hour/day[c]			0.23
<10	75 (76.5)	77 (79.4)	
≥10	23 (23.5)	20 (20.6)	
Mean±SD	6.5±3.3	6.0±3.1	0.26
Night-time sleep, hour/day[d]			0.001
<8	18 (18.8)	2 (2.1)	
8–9	45 (46.9)	31 (31.6)	
>9	33 (34.4)	65 (66.3)	
Mean±SD	8.3±1.3	8.8±1.5	0.02

SD: standard deviation
[a] Data are presented as no. (%) or mean ± standard deviation
[b] Weekday: n=90, with 4 missing; weekend: n=94
[c] Missing data: n=2 for weekday, n=3 for weekend
[d] Missing data: n=4 for weekday, n=2 for weekend

Parental perception of child health and awareness of existing lifestyle behaviour guidelines

Table 4 shows parental perceptions of their child's health. Of the parents, 20.0% and 18.0% perceived their child to be underweight and receiving inadequate calories, respectively, while 11.0% perceived their child to be overweight and receiving too much calories. There were 37.0% and 34.0% of parents who perceived their child to be receiving inadequate PA and sleep, respectively, while 73.0% expressed concerns over their child's SVT. Only 51.0% and 59.0% of parents were aware of existing PA and SVT guidelines, respectively, whereas 80.0% were aware of existing sleep guidelines.

DISCUSSION

This study gave us further insight into the lifestyle behaviours of children aged 5–14 years. Our data revealed that in a typical week, approximately 30% and 40% of the children in this age group did not engage in any vigorous or moderate PA, respectively. At least a fifth were engaged in high SB and were not receiving adequate sleep, while more than half were exceeding SVT recommendations. None of the children in this study met the recommended PA guidelines, while only 19.3% and 21.7% met both sleep and SVT guidelines on weekdays and weekends, respectively (data not shown).[7]

Children who engaged in PA spent only 2–3 days/week in moderate or vigorous PA. Our observations of low PA involvement concur with another Singapore study using self-reported PA from primary school students.[18] However, other Singapore studies have shown that engagement in PA was substantially lower when measured using heart rate monitoring data, with <15% of the primary school children[18,30] and none of the adolescents[19] meeting recommended PA guidelines. This trend of relatively low PA seems to begin as early as preschool; results from accelerometery data showed that children in Singapore aged 4.4 years spent only a median of 0.5 (interquartile range 0.3–0.8) hour/day on moderate to vigorous PA.[15] A large 12-country study (including 8 Western, 2 Asian and 2 African countries) using data from accelerometers reported that the overall adherence to moderate to vigorous PA guidelines in other Western and Asian countries in children of primary school age (9–11 years) was 44%.[31] The highest adherence was in Finland at 61%, and the lowest adherence was in China at 15%. Our findings, which included other existing Singapore-published data,[12,18,19,30]

Table 4. Parental perception on child health and parental awareness of available lifestyle guidelines (N=100)

Parental perceptions	No. (%)
Weight of child	
Normal	69 (69.0)
Underweight	20 (20.0)
Overweight	11 (11.0)
Child receiving adequate physical activity	
Yes	63 (63.0)
No	37 (37.0)
Concerns over screen viewing time of child	
Yes	73 (73.0)
No	27 (27.0)
Child receiving adequate sleep	
Yes	66 (66.0)
No	34 (34.0)
Child receiving adequate calories	
Yes	71 (71.0)
No	18 (18.0)
Yes, too much	11 (11.0)
Awareness of physical activity guidelines	
Yes	51 (51.0)
No	49 (49.0)
Awareness of sleep guidelines	
Yes	80 (80.0)
No	20 (20.0)
Awareness of screen time guidelines	
Yes	59 (59.0)
No	41 (41.0)

point to overall low PA involvement in all age groups and indicate that any interventions promoting PA in children need to begin as early as preschool. With great emphasis placed on homework, enrichments classes and long hours spent in school, more opportunities for movement and play should be incorporated into the school-based programmes.

Time spent watching television remains the most common measure of SB in children and adolescence.[25] Our findings of SVT, which ranged from 3–4 hours/day in children with a mean age of 9 years, agree with a Singapore-published survey,[32] and weekends seem to be the time when more children indulge in recreational screen time, as previously shown.[33,34] It is known that higher SVT is common in higher-income countries[31] like Singapore, where handheld devices have become increasingly accessible to young children and where most adults own their own screen devices.[35] The average SVT reported in our study was comparable to data in children aged 9–11 years from higher-income countries like the UK, US and Australia, with SVT ranging from 3.0 to 3.4 hours/day.[31] Excessive SVT appears to begin in early childhood, with 75% of Singaporean children aged 2 years exceeding the American Academy of Pediatrics recommendations of 1 hour/day limit at age 2 years,[14] once again alluding that interventions need to begin at preschool level or earlier to reduce children's SVT at a later age.

Interestingly, children in our study were engaged in longer durations of SB, with a higher proportion in high SB (>10 hours/day) during the weekdays than on weekends. These observations suggest that SVT might not be the key contributor to SB in our population.[36] Especially in Singapore, the schooling culture leans towards prolonged sitting time during lessons, followed by a very constructed after-school life filled with enrichment classes or homework that would altogether contribute to longer durations of SB on weekdays. Similar to what we have seen with PA, high SB is already apparent in preschoolers, and objective accelerometry data have shown children spending almost 8 hours per day in SB at age 4.4 years.[15] Chen et al.[1] reported a trend opposite from ours in the preschooler age group, with higher SB observed during non-school days rather than during school days. However, they did indicate that the lower SB on school days could be attributed to more regular naptimes scheduled by childcare centres, rather than an increase in PA[1].

Our survey revealed that a significantly higher proportion of children (18.8%) were receiving inadequate sleep on weekdays (<8 hours of sleep) compared with on weekends, which concurs with previous observations in Singapore adolescents.[37] Overall, evidence in preschoolers has shown that a large proportion (>85.0%) were not meeting the sleep guidelines.[12] The discrepancies in these findings between preschoolers and school-aged children could be due to the frequency and duration of naps the children were having in the day. The total sleep duration children in Singapore are receiving may be underestimated especially in younger children owing to the mandatory scheduled naptimes at childcare centres. It might be useful to account for the amount of sleep received at childcare, especially when approximately 70% of children in Singapore spend their days in full-day childcare by age 3 years,

and this number increases to 89–91% in the subsequent years.[38] While napping is more common in preschoolers,[12] 37% of children in our study's age group were still taking daily naps that lasted for 1.5 hours on average on weekdays, and for 1 hour on weekends (data not shown), which is still a significant proportion compared with that in Western countries where only 0.9% of children still slept in the daytime by 7 years of age.[39]

Compared with previous studies, in which parents tend to underestimate the amount of sleep their children require,[16,40] the parents in our study showed the most awareness for existing sleep guidelines (80%). Only 30% were concerned about the amount of sleep their children were receiving, which aligns with approximately the 20% of children who were not meeting the recommended guidelines during the weekdays. Only half of the parents were aware of the PA guidelines for children, and only 11% were concerned about their child being overweight when the proxy-reported BMI showed that 18% of the children were overweight and 11% were obese. Our findings corroborate previous studies on how it is common for parents to underestimate the amount of PA their child requires[41] and their child's weight status.[42] In contrast, while parents in this study claimed to be most aware of the guidelines for recreational SVT (approximately 60%) and were most concerned about SVT in children (approximately 70%), the percentage of children exceeding the guidelines were still high. Along with the reported high use of screen devices among adult Singaporeans,[35] a study by Bernard et al. has interestingly also shown that children's screen use behaviour at age 2–3 years was strongly influenced by parental behaviour. The results suggest that the presence of frequent screen users in the household is associated with children's screen behaviour, and thus targeting parental behaviour might be effective in reducing recreational SVT early in children.[14]

Strengths and limitations

This study managed to collect comprehensive data on the lifestyle behaviours of children in Singapore aged 5–14 years old, along with data on parental perception on their child's health and parental awareness of existing guidelines. The strength of the study lies mainly in the use of a cost-effective and efficient online method of survey data collection, which was preferred over the conventional hard-copy survey. The limitations of the survey include selection bias and limitations in generalisability due to the survey method, which uses a convenience sampling method, and the small sample size. The wide age range sampled in this study may reduce the internal and external validity of the study. Other limitations include the possibility of under-reporting, especially when parents had to report by proxy the children's lifestyle behaviours, such as SVT or PA, which might have taken place at school or when the parents are at work while the children are at home.

CONCLUSION

Findings from this study support the need for an integrated 24-hour activity guideline for children and adolescents in our Singapore population to help with better monitoring and improvement of these behaviours. The data from this study spurred the creation of the Singapore Integrated 24-Hour Activity Guidelines for Children And Adolescents.[43] The next steps would be the dissemination and implementation of these guidelines in schools so that children and parents will be aware of integrated movement-related behaviours for the benefit of long-term health and for the prevention of obesity.

Acknowledgements

We would like to thank members of the Singapore Integrated 24-Hour Activity Guidelines for Children and Adolescents Workgroup for their intellectual contribution to the development of the survey: Benny Kai Guo Loo, Benedict Chi'-Loong Tan, Michael Yong Hwa Chia, Poh Chong Chan, Dinesh Sirisena, Mohammad Ashik Zainuddin, Jean Yin Oh, Oon Hoe Teoh, Teresa Shu Zhen Tan, Micheal Chee Meng Lim, Ethel Jie Kai Lim, Falk Mueller-Riemenschneider, Ngiap Chuan Tan, Ratnaporn Siriamornsarp and Kee Chong Ng.

This research was supported by the Integrated Platform for Research in Advancing Metabolic Health Outcomes in Women and Children (IPRAMHO) - Singapore Ministry of Health's National Medical Research Council Centre Grant NMRC/CG/C008A/2017_KKH.

REFERENCES

1. Chen B, Bernard JY, Padmapriya N, et al. Associations between early-life screen viewing and 24 hour movement behaviours: findings from a longitudinal birth cohort study. Lancet Child Adolesc Health 2020;4:201-9.
2. Zhou Y, Aris IM, Tan SS, et al. Sleep duration and growth outcomes across the first two years of life in the GUSTO study. Sleep Med 2015;16:1281-6.
3. Padmapriya N, Aris IM, Tint MT, et al. Sex-specific longitudinal associations of screen viewing time in children at 2-3 years with adiposity at 3-5 years. Int J Obes (Lond) 2019;43:1334-43.
4. Janssen I, Leblanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. Int J Behav Nutr Phys Act 2010;7:40.
5. Chaput JP, Gray CE, Poitras VJ, et al. Systematic review of the relationships between sleep duration and health indicators in school-aged children and youth. Appl Physiol Nutr Metab 2016;41(6 Suppl 3):S266-82.
6. Atkin AJ, Gorely T, Clemes SA, et al. Methods of measurement in epidemiology: sedentary behaviour. Int J Epidemiol 2012; 41:1460-71.
7. Tremblay MS, Carson V, Chaput JP, et al. Canadian 24-Hour Movement Guidelines for Children and Youth: An Integration of

Physical Activity, Sedentary Behaviour, and Sleep. Appl Physiol Nutr Metab 2016;41(6 Suppl 3):S311-27.

8. Yu Q, Aris IM, Tan KH, et al. Application and utility of continuous glucose monitoring in pregnancy: a systematic review. Front Endocrinol (Lausanne) 2019;10:697.
9. Chia MYH, Tay LY, Chua TBK. Quality of life and meeting 24-h WHO guidelines among preschool children in Singapore. Early Childhood Educ J 2020;48:313-23.
10. Carson V, Janssen I. Volume, patterns, and types of sedentary behavior and cardio-metabolic health in children and adolescents: a cross-sectional study. BMC Public Health 2011;11:274.
11. Twenge JM, Campbell WK. Associations between screen time and lower psychological well-being among children and adolescents: evidence from a population-based study. Prev Med Rep 2018;12:271-83.
12. Chen B, Bernard JY, Padmapriya N, et al. Socio-demographic and maternal predictors of adherence to 24-hour movement guidelines in Singaporean children. Int J Behav Nutr Phys Act 2019;16:70.
13. Okely AD, Ghersi D, Hesketh KD, et al. A collaborative approach to adopting/adapting guidelines - The Australian 24-Hour Movement Guidelines for the early years (Birth to 5 years): an integration of physical activity, sedentary behavior, and sleep. BMC Public Health 2017;17(Suppl 5):869.
14. Bernard JY, Padmapriya N, Chen B, et al. Predictors of screen viewing time in young Singaporean children: the GUSTO cohort. Int J Behav Nutr Phys Act 2017;14:112.
15. Chen B, Waters CN, Compier T, et al. Understanding physical activity and sedentary behaviour among preschool-aged children in Singapore: a mixed-methods approach. BMJ Open 2020; 10:e030606.
16. Aishworiya R, Chan P, Kiing J, et al. Sleep behaviour in a sample of preschool children in Singapore. Ann Acad Med Singap 2012; 41:99-104.
17. Goh SN, Teh LH, Tay WR, et al. Sociodemographic, home environment and parental influences on total and device-specific screen viewing in children aged 2 years and below: an observational study. BMJ Open 2016;6:e009113.
18. Chia M. Physical inactivity among children and adolescents in Singapore: a paradoxical issue. Acta Kinesiol 2008;2:7-15.
19. Lye JCT, Mukherjee S, Chia MYH. Physical activity and sedentary behavior patterns of Singaporean adolescents. J Phys Act Health 2015;12:1213-20.
20. Yeo SC, Jos AM, Erwin C, et al. Associations of sleep duration on school nights with self-rated health, overweight, and depression symptoms in adolescents: problems and possible solutions. Sleep Med 2019;60:96-108.
21. Craig CL, Marshall AL, Sjostrom M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381-95.
22. Owens JA, Maxim R, Nobile C, et al. Parental and self-report of sleep in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 2000;154:549-55.
23. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep 2000;23:1043-51.
24. Tremblay MS, Aubert S, Barnes JD, et al. Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. Int J Behav Nutr Phys Act 2017;14:75.
25. Tremblay MS, LeBlanc AG, Kho ME, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. Int J Behav Nutr Phys Act 2011;8:98.
26. Crane JR, Naylor PJ, Temple VA. The physical activity and sedentary behaviour patterns of children in kindergarten and grade 2. Children (Basel) 2018;5:131.
27. Paruthi S, Brooks LJ, D'Ambrosio C, et al. Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. J Clin Sleep Med 2016;12:785-6.
28. World Health Organization. The Anthro Survey Analyser. Available at: https://worldhealthorg.shinyapps.io/anthro/. Accessed on 18 May 2021.
29. de Onis M, Onyango AW, Borghi E, et al. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85:660-7.
30. Gilbey H, Gilbey M. The physical activity of Singapore primary school children as estimated by heart rate monitoring. Pediatr Exerc Sci 1995;7:26-35.
31. Roman-Vinas B, Chaput JP, Katzmarzyk PT, et al. Proportion of children meeting recommendations for 24-hour movement guidelines and associations with adiposity in a 12-country study. Int J Behav Nutr Phys Act 2016;13:123.
32. The Straits Times. 12-year-olds in Singapore spend 6½ hours daily on electronic devices: survey, 2 April 2017. Available at: https://www.straitstimes.com/singapore/glued-to-screen-for-612-hours-digital-habits-in-singapore. Accessed on 18 May 2021.
33. Engberg E, Figueiredo RAO, Rounge TB, et al. Heavy screen use on weekends in childhood predicts increased body mass index in adolescence: a three-year follow-up study. J Adolesc Health 2020;66:559-66.
34. Sigmundova D, Badura P, Sigmund E, et al. Weekday-weekend variations in mother-/father-child physical activity and screen time relationship: a cross-sectional study in a random sample of Czech families with 5- to 12-year-old children. Eur J Sport Sci 2018;18:1158-67.
35. Google. Consumer barometer, November 2014. Available at: https://www.thinkwithgoogle.com/intl/en-145/consumer-insights/consumer-journey/consumer-barometer. Accessed on 18 May 2021.
36. Hoffmann B, Kobel S, Wartha O, et al. High sedentary time in children is not only due to screen media use: a cross-sectional study. BMC Pediatr 2019;19:154.
37. Lo JC, Lee SM, Lee XK, et al. Sustained benefits of delaying school start time on adolescent sleep and well-being. Sleep 2018;41:zsy052.
38. National Center on Education and the Economy. The early advantage: Singapore system at a glance, 14 October 2018. Available at: http://ncee.org/wp-content/uploads/2018/10/Singapore-at-a-Glance.pdf. Accessed on 18 May 2021.
39. Iglowstein I, Jenni OG, Molinari L, et al. Sleep duration from infancy to adolescence: reference values and generational trends. Pediatrics 2003;111:302-7.
40. Owens JA, Jones C, Nash R. Caregivers' knowledge, behavior, and attitudes regarding healthy sleep in young children. J Clin Sleep Med 2011;7:345-50.
41. Corder K, van Sluijs EM, McMinn AM, et al. Perception versus reality awareness of physical activity levels of British children. Am J Prev Med 2010;38:1-8.
42. Ruiter ELM, Saat JJEH, Molleman GRM, et al. Parents' underestimation of their child's weight status. Moderating factors and change over time: a cross-sectional study. PLoS One 2020;15: e0227761.
43. Loo BKG, Tan BCL, Chia MYH, et al. Singapore Integrated 24-Hour Activity Guidelines for Children and Adolescents. Singapore J Obstet Gynaecol 2021;52:20-31.

ORIGINAL ARTICLE

Ann Acad Med Singap 2021;50:703-11
https://doi.org/10.47102/annals-acadmedsg.2021160

Safety and side effect profile of Pfizer-BioNTech COVID-19 vaccination among healthcare workers: A tertiary hospital experience in Singapore

See Ming Lim [1]*MPH*, Hwang Ching Chan [2]*MPH*, Amelia Santosa [3]*MBBS*, Swee Chye Quek [4]*MD*, Eugene Hern Choon Liu [5,6]*MD*, Jyoti Somani [5,7]*MD*

ABSTRACT

Introduction: Vaccination remains a key strategy to living endemically with COVID-19. The Pfizer-BioNTech COVID-19 vaccine was first granted interim authorisation for use in Singapore in December 2020. With overseas studies published about the safety and side effect profiles of mRNA COVID-19 vaccines focusing mainly on non-Asian populations, we described the side effects of Pfizer-BioNTech COVID-19 vaccination experienced by the healthcare workers (HCWs) in a tertiary hospital in Singapore.

Methods: Data were obtained from the Occupational Health Clinic (OHC) at the National University Hospital in Singapore, which monitored staff for any adverse effects within 30 minutes post-vaccination on-site and any adverse effects after that. A cross-sectional study among the vaccinated HCWs was conducted using an online survey, which established basic demographics, histories of allergies or atopic disorders, and adverse events encountered after dose 1 and dose 2 of vaccination.

Results: No anaphylaxis was reported. Most common symptom was giddiness (32.7%) experienced by HCWs within 30 minutes. Adverse events attended post-vaccination by OHC were generally mild and self-limiting. From the survey, odds of experiencing an adverse event after dose 2 was significantly higher than after the first dose, especially for fever/chills (odds ratio [OR] 22.5). Fever/chills, injection site reactions, headache, aches and pains, and feeling unwell were significantly more common in HCWs below 60 years compared to those ≥60 years. An allergy to food (adjusted OR 2.7) and a history of eczema/sensitive skin (adjusted OR 2.6) were associated with a skin reaction not at injection site.

Conclusion: The side effects experienced after Pfizer-BioNTech COVID-19 vaccines are generally self-limiting and mild, with no anaphylaxis reported.

Ann Acad Med Singap 2021;50:703-11

Keywords: COVID-19, infectious diseases, occupational medicine, side effects, vaccination

INTRODUCTION

The newly emerged coronavirus virus 2019 (COVID-19) disease was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on 30 January 2020, and subsequently designated a pandemic on 11 March 2020.[1] Globally, over 209 million cases have been reported, with more than 4.4 million confirmed deaths as of 20 August 2021,[2] with numbers increasing daily.

A series of public health measures including social distancing, wearing of face masks, maintaining good personal hygiene and lockdowns have been introduced to mitigate the spread of the virus. Vaccination, however, remains a key strategy for sustained protection, and living endemically with the virus.[3]

On 11 December 2020, the US Food and Drug Administration issued the first emergency use authorisation for the BNT162b2 COVID-19 vaccine

[1] Occupational Health Clinic, National University Hospital, Singapore
[2] Epidemiology Unit, National University Hospital, Singapore
[3] Division of Rheumatology, Department of Medicine, National University Hospital, Singapore
[4] Chairman Medical Board's Office, National University Hospital, Singapore
[5] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[6] Department of Anaesthesia, National University Hospital, Singapore
[7] Division of Infectious Diseases, Department of Medicine, National University Hospital, Singapore
Correspondence: Dr See Ming Lim, Occupational Health Clinic, National University Hospital, 5 Lower Kent Ridge Road, Main Building, Level 1, Singapore 119074.
Email: see_ming_lim@nuhs.edu.sg

CLINICAL IMPACT

What is New

- This study describes the safety and side effect profile of Pfizer-BioNTech COVID-19 vaccination of the healthcare population in Singapore.
- Side effects are generally self-limiting and mild, similar to trials done overseas that comprise mainly non-Asian participants.

Clinical Implications

- The benefits of vaccination against acquiring COVID-19 infection and its possible complications outweigh the side effects experienced.
- The results from this paper can be used to encourage more to take up COVID-19 vaccination.

developed by Pfizer and BioNTech in individuals aged 16 years and above.[4] The Pfizer-BioNTech COVID-19 vaccine belongs to a novel category of vaccines called messenger ribonucleic acid (mRNA) vaccines. mRNA vaccines deliver segments of mRNA that encode for a protein, which in the case of the COVID-19 mRNA vaccines, is a code for the spike protein found on the surface of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. mRNA is highly degradable, and so these mRNA vaccines have been designed to deliver the mRNA material within liposomes for protection. These liposomes, which contain polyethylene glycol and various other excipients, are highly immunogenic and are thought to be responsible for the strong local and systemic side effects reported in patients. SARS-CoV-2 enters the host airway mucosal cells via the attachment of its spike protein to the host's ACE-II receptor, thus, antibodies to the spike protein are induced by the vaccine, allowing for protection against future infection.[5,6]

There have been concerns among the public and even among health professionals about the safety profile of mRNA vaccines, given that they are new to the market. In the clinical trials of Pfizer-BioNTech COVID-19 vaccines, frequently reported reactions were pain at the injection site, fatigue and headache, which were usually short-term. Systemic reactions were more common and severe after the second dose than after the first dose, and were generally more common in those under the age of 55 compared to older recipients. The incidence of serious adverse events was low and was similar in both vaccine and placebo groups.[7]

Singapore was the first country in Asia to receive the vaccine on 21 December 2020, and as in many countries, healthcare workers (HCWs) were prioritised to be vaccinated by the Ministry of Health (MOH). However, there remains limited data and literature on the side effects of the Pfizer-BioNTech COVID-19 vaccines that focus on the healthcare population in Asia. Therefore, the objective of this study was to analyse the safety and side effect profile of the Pfizer-BioNTech COVID-19 vaccines among HCWs at the National University Hospital (NUH) in Singapore. The Occupational Health Clinic (OHC) in the tertiary hospital is responsible for administering and monitoring vaccination in newly hired HCWs as well as ensuring timely vaccination updates of all employees. With support from infectious diseases (ID) and allergy specialists, OHC implemented the same institutional processes to monitor HCWs post-vaccination for the COVID-19 staff vaccination exercise. In addition to 30-minute monitoring post-vaccination on-site, part of the surveillance included a self-reported online survey questionnaire.

METHOD

OHC is an in-house clinic within the hospital, which manages work-related health and safety issues of more than 7,600 HCWs to ensure a safe and healthy work environment. OHC, with support from human resources, operations and ID specialists, proactively stepped up its actions at the start of the COVID-19 pandemic to protect staff from contracting COVID-19 at work. Actions included screening and monitoring fitness for work; active redeployment of staff with medical conditions that put them at increased risk of more complicated COVID-19 infection; surveillance of staff health post-exposure; and return-to-work assessment for staff with acute respiratory illnesses.

Working in close collaboration with various medical specialists, nursing, pharmacy and operations teams, OHC officially rolled out the staff COVID-19 vaccination exercise on 11 January 2021, as an important tool to protect the safety and health of staff against COVID-19, in line with organisation and national directives. Some contraindications as listed by MOH then included immunocompromised conditions, prior anaphylaxis/severe allergy and pregnancy (see Supplementary Online Materials), which were gradually allowed vaccination as the vaccination exercise continued.

Monitoring of adverse effects within 30 minutes post-vaccination

Guidelines from MOH regarding vaccine preparation, administration, contraindications and side effects were followed,[8] with a mandatory 30-minute observation period post-vaccination on-site for adverse effects. If any staff developed any symptoms or discomfort during this period, they would be moved to a treatment room for vital sign monitoring and assessment by an OHC doctor. Based on assessment, unwell staff might be observed for a longer period of time, for example, additional 30 minutes to allow the symptoms to subside. Staff would be transferred to the emergency department (ED) for further evaluation if the symptoms were deemed serious based on initial assessment, for example, severe allergic reactions, or no improvement after extended period of observation.

Monitoring of adverse effects post-vaccination

OHC was also responsible for the recording and reporting of any early or late adverse effects and allergic reactions. HCWs were asked to report any symptoms or reactions that occurred later after leaving the vaccination clinic to OHC via calls, emails or walk-in consults. For common side effects such as fever or body ache post-vaccination, appropriate medical advice was given based on MOH guidelines.[8] Staff with potential allergic reactions or prolonged/severe side effects were reviewed by OHC doctors and these problems were reported to MOH. For rashes or side effects that could indicate allergy, OHC and an allergy specialist would evaluate and decide whether a second dose could be given.

Monitoring of adverse effects via online survey

A cross-sectional study was conducted when HCWs being monitored on-site after the second dose were invited to participate voluntarily in a survey hosted on the form.sg platform, a government-initiated, secure internet database. The questions in part 1 of the survey established basic demographics, histories of allergies (food, medication or vaccines) or atopic disorders (allergic rhinitis, asthma or eczema), and adverse events encountered after the first dose. Those who completed part 1 would be invited to participate in part 2 of the survey 1 week after second dose was administered. Questions in the second part were similarly phrased as those in the first part and included demographics and adverse events encountered after the second dose. Survey responses were collected for a duration of 2 months, between 8 February and 12 April 2021 and analysed using STATA version 13.0 (StataCorp, College Station, US).

Only participants who completed both part 1 and part 2 of the survey were included in the analysis. We used the number of staff who completed 2 doses as the denominator as all were invited to participate post-vaccination (Fig.1). Participants' demographics were descriptive in nature, presented as frequencies and percentages. Differences in responses between the first dose and second dose were compared using McNemar's test of symmetry. Chi-square test was used in hypothesis testing to investigate if there were differences in adverse events reported by different age groups, self-reported histories of allergies (food, medication or vaccines) and atopic disorders (allergic rhinitis, asthma or eczema). We used age strata <60 years versus ≥60 years, in line with the national definition of seniors prioritised for receiving COVID-19 vaccinations. Logistic regression was performed with each adverse effect as the dependent variable and a history of allergies or atopic disorders as the independent variable, with crude and adjusted odds ratio (for sex and age as a continuous variable). A P value <0.05 was considered statistically significant.

This study was exempted from ethics review by the National Healthcare Group, Domain Specific Institutional Review Board (NHG DSRB reference number 2021/00572).

RESULTS

Adverse effects attended to at vaccination clinic and at OHC

The 3 most common symptoms attended to within the 30-minute observation period at the vaccination clinic

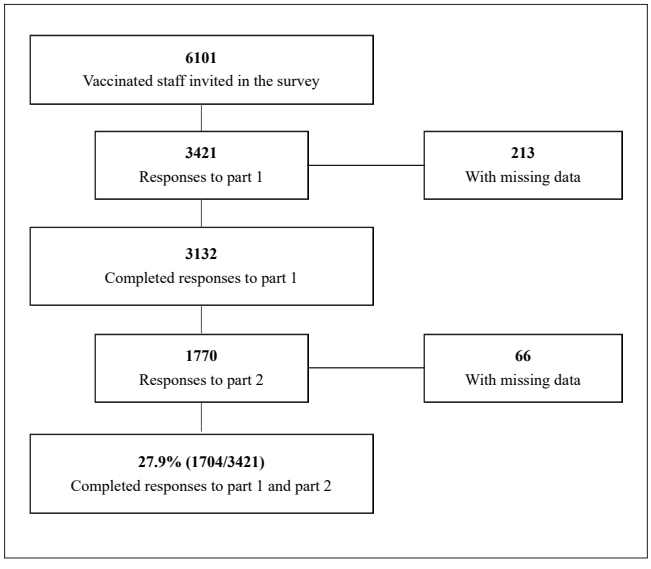


Fig. 1. Flowchart of survey respondents included in the analysis.

Table 1. Symptoms attended to at the vaccination clinic

Symptoms attended	Staff, no. (%) N=196	Disposition
Giddiness	64 (32.7)	58 discharged from vaccination clinic 6 transferred to ED and discharged after observation
Rashes/itch	46 (23.5)	43 discharged from vaccination clinic 3 transferred to ED and discharged after observation
Palpitation/chest discomfort	29 (17.2)	28 discharged from vaccination clinic 1 transferred to ED and admitted for further evaluation
Numbness over injection arm	16 (8.2)	16 discharged from vaccination clinic
Headache	11 (5.6)	10 discharged from vaccination clinic 1 transferred to ED and discharged after observation
Nausea/vomitting/reflux	11 (5.6)	9 discharged from vaccination clinic 2 transferred to ED and discharged after observation
Throat discomfort	9 (4.6)	9 discharged from vaccination clinic
Sensation of breathlessness	4 (2.1)	3 discharged from vaccination clinic 1 transferred to ED and discharged after observation
Eye conditions, e.g. blurred vision	3 (1.5)	3 discharged from vaccination clinic
Others	3 (1.5)	3 discharged from vaccination clinic

ED: Emergency department

were giddiness (32.7%), rashes/itch (23.5%) and palpitation/chest discomfort (17.2%). Most staff who experienced any symptoms improved within 30 minutes of further monitoring. However, of 196 staff requiring such care after vaccination, 16 (8.2%) of them had to be transferred to ED for further evaluation and management. No staff had anaphylaxis (Table 1).

OHC attended to a total of 329 staff at the end of the staff vaccination exercise. The most common adverse effects attended to were fever/chill (26.1%), rashes/itch/eye swelling (21.3%), myalgia (9.4%), swelling/pain over injection site (7.6%), giddiness (6.1%) and headache (6.1%).

Of all the 525 staff reviewed at OHC and vaccination clinic, 28 staff were advised to withhold their second doses due to angioedema (35.7%), urticaria (35.7%), pregnancy (25.0%) and retinal clots/hypertension (3.6%), while 10 other staff were advised against future doses due to angioedema (50.0%) and urticaria (50.0%) after second dose. The pregnant staff were subsequently allowed to complete dose 2 after MOH revised its guidance.[9]

Adverse reactions reported from survey

A total of 3,421 out of 6,101 vaccinated staff responded to part 1 of the survey, of which 1,704 completed part 2 as well, giving a response rate of 27.9% (Fig. 1). Among the respondents to the survey, those 18–50 years of age accounted for the large majority (87.4%), while those 51–80 years old made up the remaining 12.6%. Respondents' median age was 35 years old, with a range of 18–76 years. The ethnicity of those who responded to the survey also corresponded proportionally with the overall makeup of the healthcare workers in our institution, with Chinese making up the majority ethnicity at 55.6%. There were also more female respondents (78.6%) than male, which relates proportionally to the overall gender ratio in our hospital settings (Table 2). At the time of vaccination, no HCWs in this study were documented to have had COVID-19.

A majority of respondents reported localised injection site reactions, with more experiencing such reactions after dose 2 (70.1%) compared to dose 1 (57.2%). Feeling unwell in general, having aches and pains, headache, and fever or chills were also commonly reported symptoms (Table 3). Although anaphylaxis was included in the survey as a symptom, none of the respondents experienced this as an adverse event. The odds of experiencing an adverse event after the second dose was significantly higher than after the first dose. Although all adverse events were reported significantly more likely after the second dose, having fever/chills was the most striking, with an odds ratio of 22.5 on the second dose, compared to the first.

Among the adverse events included in the survey, having fever or chills, injection site reactions, headache,

Table 2. Demographics of survey respondents

	Numbers responded (N=1704)	Percentage of respondents (%)
Age group (years)		
18–30	494	29.0
31–40	649	38.1
41–50	346	20.3
51–60	160	9.4
61–70	50	2.9
71–80	5	0.3
Sex		
Female	1340	78.6
Male	364	21.4
Ethnicity		
Chinese	948	55.6
Malay	198	11.6
Indian	174	10.2
Eurasian	9	0.5
Others	375	22.0
Job groups		
Administration	194	11.4
Allied health	323	19.0
Ancillary	151	8.9
Medical/Dental	203	11.9
Nursing	693	40.7
Service partners	50	2.9
MOHH doctors	16	0.9
Others	74	4.3

MOHH: Ministry of Health Holdings

generalised aches and pains and feeling unwell were significantly more common in the younger age group. The survey showed 47.2% of respondents below 60 years reported fever or chills after dose 1 and/or dose 2, compared to 25.0% in those aged 60 and above (P<0.01). A majority (78.5%) of those in the age group below 60 years reported an injection site reaction, while the prevalence among those 60 years and above was comparatively lower at 47.1% (P<0.01). Feeling unwell, aches and pains, and headache were also symptoms more significantly reported in those below 60 years, compared to those 60 years and above (Fig. 2).

Among survey respondents who self-reported an allergy (food, medication or vaccines) or atopic disorders (allergic rhinitis/sensitive nose, asthma, or eczema/sensitive skin), an allergy to food, and a history of eczema/sensitive skin were the only 2 conditions associated with a higher odds ratio of skin reaction not at the injection site (rash, hives, urticaria or itch). After adjusting for age and gender, the odds ratio of respondents with an allergy to a food and reporting a skin reaction post-vaccination was 2.7 that of those without any food allergy, while the odds ratio of respondents with eczema/sensitive skin was 2.6 that of respondents who reported no eczema/sensitive skin (Table 4). Both were statistically significant.

DISCUSSION

This study aimed to analyse the safety and side effect profile of the Pfizer-BioNTech COVID-19 vaccines among HCWs at NUH in Singapore. Based on the survey results, localised injection site reactions (rash, redness, swelling and pain) were the most common, followed by systemic reactions such as feeling unwell in general (fatigue, tiredness and weakness) and aches and pains (joint pain, muscle pain and body ache). Reactions were generally self-limiting in nature and were reported more often after dose 2 than dose 1, and in the younger age group compared to the older age group. The findings were consistent with those observed in studies conducted overseas and reports of suspected adverse events in Singapore as well.[7,10,11]

No anaphylaxis of HCWs vaccinated in the hospital was reported as of 24 August 2021. As of 31 July 2021, the incidence of anaphylaxis reported in Singapore with the mRNA vaccines was about 0.86 per 100,000 doses administered, similar to those reported overseas of around 0.5 to 2 per 100,000.[11,12] We reported no cases of myocarditis/pericarditis.

Since mRNA vaccination started in Singapore, MOH had taken a more conservative stance with more contraindications and precautions for who could be vaccinated initially (see Supplementary Online Materials). With the emergence of international data from real-world vaccination roll-outs, contraindications were gradually relaxed after no major safety concerns were noted. For example, persons with history of allergic reactions (excluding to vaccines) not amounting to an anaphylaxis were allowed to be vaccinated after 12 March 2021, while those with history of anaphylaxis were excluded until 5 June 2021,[13] after no evidence to suggest that a prior history of anaphylaxis would predict the development of anaphylaxis to the mRNA COVID-19 vaccines.

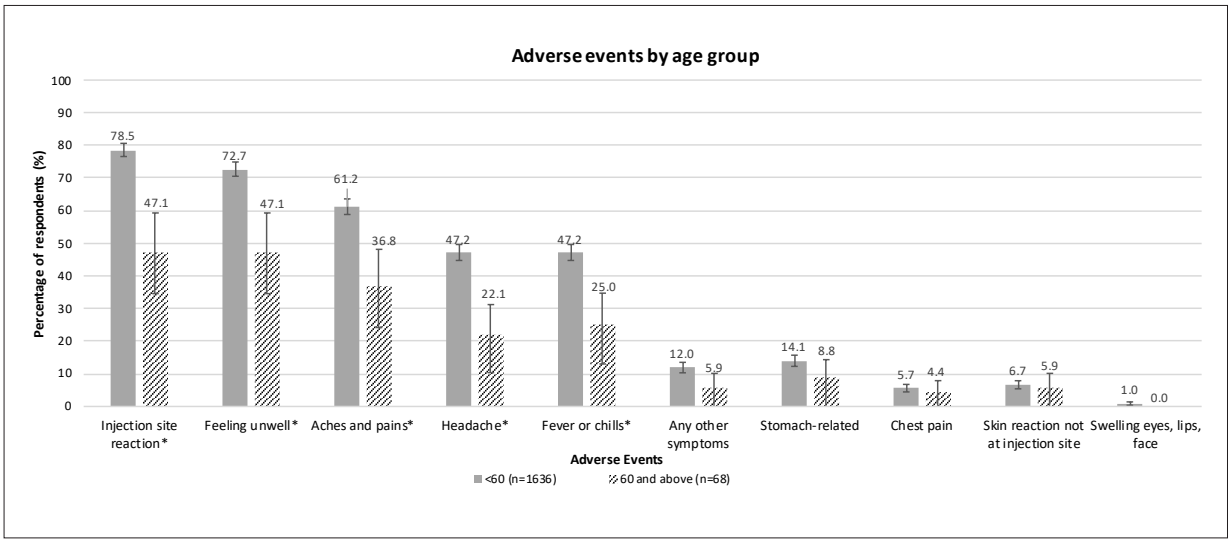


Fig. 2. Adverse events reported after dose 1 and/or dose 2, by age group.
*Significantly different proportions between respondents aged <60, and those aged 60 and above, who reported the specified adverse effect (chi-squared test for statistical significance, $P<0.01$)
I bars represent 95% confidence intervals, and number labels indicate the percentage of participants who reported the stated adverse event.

Table 3. Comparison of adverse reactions reported after dose 1 and dose 2

Adverse reaction	After dose 1 Staff, no. (%) N=1704	After dose 2 Staff, no. (%) N=1704	McNemar's odds ratio (95% confidence interval)
Injection site reaction (rash, redness, swelling, pain)	975 (57.2)	1195 (70.1)	2.8 (2.3–3.5)
Feeling unwell in general (fatigue, tiredness, weakness)	626 (36.7)	1127 (66.1)	6.3 (5.1–8.0)
Aches and pains (joint pain, muscle pain, body ache)	512 (30.1)	885 (51.9)	3.7 (3.0–4.4)
Headache	321 (18.8)	711 (41.7)	6.1 (4.8–7.9)
Fever or chills	159 (9.3)	761 (44.7)	22.5 (15.4–34.1)
Chest pain, palpitations (abnormal heartbeat), breathlessness	43 (2.5)	66 (3.9)	1.78 (1.1–2.9)
Stomach-related (diarrhoea, nausea, vomiting, stomach discomfort)	73 (4.3)	199 (11.7)	4.4 (3.1–6.5)
Swelling of the eyes, lips or face	3 (0.2)	13 (0.8)	4.3 (1.2–23.7)
Skin reaction, not at injection site (rash, hives, urticaria, itch)	42 (2.5)	90 (5.3)	3.0 (1.9–5.0)
Any other symptoms	90 (5.9)	140 (8.2)	1.8 (1.3–2.6)

A self-reported history of allergy to food and eczema/sensitive skin were associated with a higher odds ratio of patient-reported skin reaction not at injection site (rash, hives, urticaria or itch), after adjusting for age and gender. As the nature of the previous allergies and the current reactions were reported by the staff themselves, it is difficult to comment whether this association is truly mediated by an allergic predisposition,

Table 4. Effect of allergy/atopic disorders on skin reaction and face swelling post-vaccination

	Skin reaction not at injection site (rash, hives, urticaria, itch)			Swelling of eyes, lips, face		
	Proportion of respondents (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)	Proportion of respondents (%)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
Allergies						
Allergy to food (n=85)	15.3	2.7 (1.5–5.1)[b]	2.7 (1.4–5.0)[b]	0	–	–
No allergy to food (n=1619)	6.2			1.0		
Allergy to medication (n=185)	5.4	0.8 (0.4–1.5)	0.8 (0.4–1.5)	1.1	0.8 (0.4–1.5)	0.8 (0.4–1.5)
No allergy to medication (n=1519)	6.8			0.9		
Allergy to vaccines (n=9)	11.1	1.8 (0.2–14.1)	1.5 (0.2–12.4)	0	–	–
No allergy to vaccines (n=1695)	6.7			0.9		
Atopic disorders						
Allergic rhinitis/sensitive nose (n=322)	9.0	1.5 (0.9–2.3)	1.4 (0.9–2.3)	1.2	1.4 (0.5–4.5)	1.4 (0.4–4.4)
No allergic rhinitis/sensitive nose (n=1382)	6.2			0.9		
Asthma (n=183)	9.8	1.6 (0.9–2.8)	1.6 (0.9–2.8)	1.1	1.2 (0.3–5.3)	1.2 (0.3–5.4)
No asthma (n=1521)	6.3			0.9		
Eczema/sensitive skin (n= 287)	12.9	2.6 (1.7–3.9)[b]	2.5 (1.7–3.9)[b]	0.7	0.7 (0.2–3.1)	0.7 (0.2–3.1)
No eczema/sensitive skin (n= 1417)	5.4			1.0		

[a] Adjusted for age as a continuous variable and sex
[b] Statistically significant odds ratio *(P*<0.01)

or whether patients may suffer from other pre-existing conditions such as chronic urticaria or anxiety, which may confound the interpretation of the reactions.[14,15]

Overall, the approach we took to monitor for adverse events for the staff vaccination exercise was safe and in line with MOH guidelines, particularly considering that it was rolled out in the context of an Emergency Use Approval as a very new type of vaccine with little prior clinical experience especially among Asian population, with only 4.3% included in phase 2/3 trials.[7] On-site monitoring for adverse effects within 30 minutes of vaccination is sufficient for diagnosis and treatment of early onset allergic reactions or anaphylaxis. The observation of frequent giddiness, palpitation/chest discomfort and headache post-vaccination also led to staff being reminded to adhere to their chronic medications and hydrate appropriately early on the day of vaccination.

After leaving the vaccination clinic, HCWs with any adverse effects were encouraged to report to OHC via phone call, email or walk-in consults. Those with common adverse effects such as fever, myalgia or pain over the injection sites were given post-vaccination management advice as per MOH guidelines.[8] Staff with potential allergic reactions or prolonged/severe side effects were reviewed as a walk-in consult at OHC. HCWs were encouraged to take photos of any visible reaction (such as rashes) to show them during these consultations. All staff who presented in this manner were reviewed by the same OHC specialist in the clinic, and also evaluated by a single allergy specialist. This would allow objective reporting and reduce observation bias between cases.

By the end of the vaccination exercise on 26 March 2021, nearly 80% (6,101 out of 7,671) of staff had completed both doses of the vaccine and subsequent vaccination of staff was by appointment only. When Singapore experienced a surge of community cases end April 2021, walk-in slots were made available for staff, which subsequently coincided with MOH's loosening of the list of contraindications to vaccination. With this, staff vaccination rates reached 94% as of 24 August 2021. While these conditions were gradually relaxed, it likely impacted vaccine acceptance, particularly among pregnant and breastfeeding HCWs and those trying to conceive, as 86 (25.3%) out of 340 staff who remained unvaccinated gave pregnancy-related reasons and breastfeeding for why they were not vaccinated.

Unvaccinated staff had to be managed carefully. At the start of the pandemic, staff with chronic medical conditions that put them at increased risk of more complicated COVID-19 infection were already redeployed to non-COVID-19 patient areas.[16] Strict compliance to personal protective equipment (PPE) and hand hygiene was enforced regularly. Similarly, unvaccinated staff were placed in lower risk areas with an emphasis on PPE compliance, while efforts to get more staff vaccinated were ongoing.

With evidence that immunity may decline over time, the Expert Committee on COVID-19 Vaccination in Singapore had recommended an additional mRNA COVID-19 vaccine dose for the immunocompromised and seniors.[17] However, in the US, HCWs who were vaccinated earliest in the vaccination roll-out would be eligible for booster dose as well.[18] Further research may be required to determine the optimal timing of the booster for HCWs that will ensure maximal protection exceeds the risk of untoward side effects.[19]

This study has a few limitations. Participation rate with valid responses was 27.9% for this self-reporting survey. It is possible that those who did not participate have milder adverse reactions compared to those who participated. Also as the first part was administered 3 weeks after the first dose, and the second part a week after dose 2, the time between experiencing the effects and the collection of participants' responses to the survey could lead to recall error. We had tried to minimise this by constructing survey questions that were well-defined and easily understood, and piloted this among a convenient sampling of healthcare workers. Even then, we identified this as a limitation, and took into consideration other studies in conjunction with our findings, before drawing conclusions from our survey results.

CONCLUSION

In conclusion, the side effects experienced after Pfizer-BioNTech COVID-19 vaccines are generally self-limiting and non-severe, with no anaphylaxis reported among the HCWs in NUH, Singapore. The benefits of vaccination against acquiring COVID-19 infection and its possible complications far outweigh the self-limiting side effects experienced. However, further studies to determine the longer-term adverse effects of this relatively new vaccine would enable individuals to make a more confident informed choice, and lend more evidence to guide public health practitioners on vaccination policy for the wider population.

Acknowledgements

We thank our fellow healthcare colleagues from nursing, pharmacy, operations centre, administration and the Occupational Health Clinic who operated the staff vaccination clinic in National University Hospital. We also thank our senior management for their support.

REFERENCES

1. World Health Organization. Rolling updates on coronavirus disease (COVID-19), 31 July 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. Accessed on 22 August 2021.
2. World Health Organization. Coronavirus disease (COVID-19) pandemic. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAjwyIKJBhBPEiwAu7zll4HKIeSbTVhCS3oiq33vDRMtwYyLXUqZuhy1y7zl9wCea6W16tM56BoCWGkQAvD_BwE. Accessed on 22 August 2021.
3. World Health Organization. COVID-19 vaccines. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines. Accessed on 22 August 2021.
4. US Food and Drug Administration. Pfizer-BioNTech COVID-19 Vaccine, 23 August 2021. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/pfizer-biontech-covid-19-vaccine. Accessed on 22 August 2021.
5. Centers for Disease Control and Prevention. mRNA vaccines, 4 March 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mRNA.html. Accessed on 22 August 2021.
6. Banerji A, Wickner PG, Saff R, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. J Allergy Clin Immunol Pract 2021;9:1423-37.
7. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383:2603-15.
8. Ministry of Health, Singapore. COVID-19 vaccination. Available at: https://www.moh.gov.sg/covid-19/vaccination. Accessed on 22 August 2021.
9. Ministry of Health, Singapore. Expert Committee on COVID-19 Vaccination expands medical eligibility for mRNA vaccines, 31 May 2021. Available at: https://www.moh.gov.sg/news-highlights/details/expert-committee-on-covid-19-vaccination-expands-medical-eligibility-for-mrna-vaccines. Accessed on 1 September 2021.
10. Kadali RAK, Janagama R, Peruru S, et al. Side effects of BNT162b2 mRNA COVID-19 vaccine: A randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers. Int J Infect Dis 2021;106:376-81.
11. Health Sciences Authority, Singapore. HSA's Safety Update #4 - COVID-19 vaccines (30 December 2020 – 31 July 2021), 31 July 2021. Available at: https://www.hsa.gov.sg/docs/default-source/hprg-vcb/safety-update-on-covid19-vaccines/hsa-safety-update-no-4-on-covid-19-vaccines-(31-july-2021).pdf. Accessed on 1 September 2021.
12. Shavit R, Maoz-Segal R, Iancovici-Kidon M, et al. Prevalence of Allergic Reactions After Pfizer-BioNTech COVID-19 Vaccination Among Adults With High Allergy Risk. JAMA Netw Open 2021;4:e2122255.
13. Ministry of Health, Singapore. Safety of mRNA vaccines in persons with anaphylaxis. Available at: https://www.moh.gov.sg/news-highlights/details/safety-of-mrna-vaccines-in-persons-with-anaphylaxis. Accessed on 1 September 2021.

14. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet 2020;396:345-60.

15. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol 2014;133:291-307.

16. Hwang J, Yong E, Cheong K, et al. Responding to the COVID-19 pandemic: The role of occupational health services in a tertiary hospital in Singapore. J Occup Health 2020;62:e12172.

17. Ministry of Health, Singapore. Expert Committee on COVID-19 Vaccination recommends an additional dose of mRNA COVID-19 vaccine for immunocompromised and seniors, 3 September 2021. Available at: https://www.moh.gov.sg/news-highlights/details/expert-committee-on-covid-19-vaccination-recommends-an-additional-dose-of-mrna-covid-19-vaccine-for-immunocompromised-and-seniors_3Sep2021. Accessed on 5 September 2021.

18. US Department of Health and Human Services. Joint Statement from HHS Public Health and Medical Experts on COVID-19 Booster Shots, 18 August 2021. Available at: https://www.hhs.gov/about/news/2021/08/18/joint-statement-hhs-public-health-and-medical-experts-covid-19-booster-shots.html. Accessed on 5 September 2021.

19. Centers for Disease Control and Prevention. Overview of data to inform recommendations for booster doses of COVID-19 vaccines, 23 June 2021. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/06-COVID-Oliver-508.pdf. Accessed on 4 September 2021.

COMMENTARY

Ann Acad Med Singap 2021;50:712-6
https://doi.org/10.47102/annals-acadmedsg.2021225

An armed assailant in our hospital: Are we prepared?

Sohil Pothiawala [1] *FAMS (EM)*, Rabind Charles [1] *FAMS (EM)*, Wai Kein Chow [2], Kheng Wee Ang [2], Karen Hsien Ling Tan [3], Mohan Tiru [1] *FAMS (EM)*

ABSTRACT

While armed assailant attacks are rare in the hospital setting, they pose a potential risk to healthcare staff, patients, visitors and the infrastructure. Singapore hospitals have well-developed disaster plans to respond to a mass casualty incident occurring outside the hospital. However, lack of an armed assailant incident response plan can significantly reduce the hospital's ability to appropriately respond to such an incident. The authors describe various strategies that can be adopted in the development of an armed assailant incident response plan. Regular staff training will increase staff resilience and capability to respond to a potential threat in the future. The aim of this article is to highlight the need for the emergency preparedness units of all hospitals to work together with various stakeholders to develop an armed assailant incident response plan. This will be of great benefit for keeping healthcare facilities safe, both for staff as well as for the community.

Ann Acad Med Singap 2021;50:712-6

Keywords: Armed assailant, hospital, preparedness, response, strategies

Armed assailant attack in a healthcare facility poses a unique risk to patients, staff and infrastructure alike. According to the US Department of Homeland Security, an armed assailant incident is defined as one where an individual is actively engaged in killing or attempting to kill people in a confined and populated area.[1]

The incidence of armed assailant attacks has been increasing in the US and other parts of the world.[2,3] Within the healthcare facility, attacks in the emergency department (ED) accounted for roughly one-third of healthcare facility incidents.[2] While these events are relatively rare in Singapore, the Singapore Terrorism Threat Assessment Report by the Ministry of Home Affairs dated 23 June 2021 continues to classify the country's terrorism threat as high; and warned that Singapore remains vulnerable to attacks against soft targets by lone actors using available objects.[4] Although there have not been any reported terrorist attacks on Singapore EDs so far, there have been incidents where healthcare staff in the ED have been threatened by patients using various objects such as penknife. In 2015, a police officer was injured in a shooting incident at the ED of Khoo Teck Puat Hospital. A suspect brought in by the police to seek medical care allegedly grabbed the policeman's gun and 3 shots were fired during the struggle. In 2002, a knife-wielding motorcycle thief was shot by the police when he charged at officers in the car park of Mount Alvernia hospital. A gang-related incident in the ED of Singapore General Hospital saw some people with parangs (machetes) attack another person.

ED is vulnerable to armed assailants as it is a public entry portal to the hospital that allows easy and 24-hour accessibility. Targeting the ED can lead to potentially higher casualties and delay in the care of existing patients. Healthcare institutions in general incorporate multiple buildings, offices, parking areas and other facilities, as well as integrate with the surrounding community and public transport facilities. Such openness makes healthcare organisations vulnerable to external incursions.

In the past, all EDs of public hospitals in Singapore housed a police post manned around-the-clock. However, this police presence has since been withdrawn and

[1] Department of Emergency Medicine, Woodlands Health Campus, Singapore
[2] Emergency Preparedness Unit, Woodlands Health Campus, Singapore
[3] Clinical Operations, Woodlands Health Campus, Singapore
Correspondence: Dr Sohil Pothiawala, Department of Emergency Medicine, Woodlands Health, 2 Yishun Central 2, Singapore 768024.
Email: sohil_pothiawala@whc.sg

outsourced to security agencies. The security personnel are stationed not just in the ED, but also other areas of the hospital. The potential threat from an armed assailant can occur in any part of the hospital where these officers may not be present at a particular time. Lack of a dedicated response protocol to an armed assailant, both in the ED and hospital premises, can significantly impact and reduce the hospital's resilience to appropriately handle such an incident. This article aims to highlight the need for all hospitals to work together with various internal and external stakeholders to develop an armed assailant incident response plan.

Hospitals have well-developed disaster plans to respond to mass casualty incidents (MCI) occurring outside the hospital environment. Most hospital staff receive emergency preparedness training to respond to MCI as part of their job scope, either through online modules or participation in disaster drills. However, an armed assailant in the ED or anywhere in the hospital poses a unique problem as existing plans may not be effective.

The random, short-lasting but violent nature of an armed assailant incident makes healthcare response extremely challenging.[3] Besides dealing with the assailant, managing the safety of the public and healthcare staff must be paramount during the incident. Because of the dynamic and unpredictable nature of an attack, there is no single best practice. The primary objectives of a response plan are:

- threat assessment and pre-incident planning,
- initiating immediate response during an incident to minimise the assailant's access to potential victims and damage, and
- post-incident recovery and support plans.

Pre-incident planning

At the very onset, assessment of threat of an armed assailant in a healthcare facility should be carried out, followed by development of a response action plan that establishes the objectives and courses of action. The plan should have input from various stakeholders, including hospital leadership, emergency preparedness unit, medical and nursing staff, security, facility engineering, human resources, law enforcement agencies and legal team. The security of the workplace can be strengthened by adopting a multitiered approach:

- Develop – proactive protective security posture
- Deter – using physical and electronic security measures
- Detect – using alert and visual detection systems
- Delay – putting up measures in place to limit movement of the offender
- Deny – Access to potential victims

Besides incorporating these aspects, an effective response plan should include:

- Data gathering and situational assessment.
- Consideration of security screening system at entrance.
- Closed-circuit television (CCTV) systems connected to the security office for surveillance.
- Restricting access by ensuring appropriate staff identification and areas being accessible with keypad coded doors.
- Early identification of threat by staff.
- Emergency alert notification to Hospital Security Command Centre as well as Singapore Police Force (SPF).
- Lockdown decision matrix for individual departments and buildings.
- Evacuation policy and procedure for patients, visitor and staff; including escape routes and safe areas marked on floor plans.
- Select effective shelter locations for those unable to escape.
- Prior coordination and sharing of plans with first responders and SPF.

During the incident

Initial assessment and action to an armed assailant situation

The first challenge is to change the healthcare staff's perspective from ignoring the possibility of such an event to proactively increasing individual awareness and being ready to respond to this situation.[5] An effective response plan enables the staff to overcome this denial and respond immediately. Staff need to be trained to be more aware of their surroundings, and identify individuals who pose a potential risk in committing a violent act. They must be empowered to immediately raise their concern to hospital security and the police, if required. Banks have alarm buttons behind counters to activate emergency response in the event of a bank robbery. Similarly, hospitals may want to consider installation of similar silent alarm buttons that contact the hospital security centre or SPF. Thus, if an armed assault is in progress, the staff can rapidly activate the emergency notification alert system to help save lives by keeping people out of harm's way, as

well as triggering a rapid response by the various stakeholders involved. Timely information is crucial, so staff should be trained to contact the police and convey key information such as the location of incident, description and number of attacker(s), type of weapons and other details.

There must be a plan in place so that the public announcement system can inform the building occupants of a potential security threat. This message must also be broadcasted to all security personnel using dedicated communication channels. The emergency notification system should also be equipped to alert people at remote locations within the hospital building or campus, advising them to keep away from the areas under threat. Hospitals can also work with SPF to use the SMS Public Alert System (number 71250) launched by the Ministry of Home Affairs in 2016, which can immediately send one-way SMS to all mobile phone users in the vicinity of this emergency.

All hospitals in Singapore have CCTV systems at various locations. These devices may also be installed at various entry/exit points, perimeter and other critical areas of the hospital to provide live feed for such threats. The system should be connected to the hospital's main security office to enable round-the-clock monitoring and surveillance. The person in charge of monitoring the CCTVs should keep building occupants and security officers updated on the movement and location of the attacker(s) by using the public announcement system and dedicated messaging services, respectively.

Upon activation of alert, there must be a centrally controlled dynamic lockdown matrix for individual areas of the hospital, including lifts and care areas. This approach will help contain the armed assailant within a limited zone, allowing other people in that building to evacuate. Non-impacted zones such as the waiting areas and cafeterias should be evacuated. Plan should also entail a detailed evacuation policy made known to all staff, with escape routes, floor plans and safe areas. A back-up evacuation route and location must be planned in case the primary route cannot be used due to assailant presence.

Immediate response model

According to the law enforcement agencies in US, the response model with an effective impact to protect people during these events has been labelled as "Avoid, Deny, Defend" (also known as "Run, Hide, Fight").[6]

- Run: The first response is to run away from the assailant, evacuate the area, and once safe, call local law enforcement agency.
- Hide: If the staff and/or patients cannot be evacuated, they should find a place to hide, turn off light and mobile devices and remain quiet. They should lock the door and use nearby equipment and furniture to reinforce the barricade, as this will deny access to the assailant.
- Fight: As a last resort, if there is an imminent danger to life, they can attempt to incapacitate the assailant by using physical aggression, either alone or with team members, or using items that can serve as an improvised weapon.

The Australia-New Zealand Counter Terrorism Committee (ANZCTC) has proposed the model of "Escape, Hide and Tell".[7] Ontario Hospital Association, Canada has also adopted a similar model of "Evacuate, Hide, Survive and Call".[8] SGSecure, Singapore's community response to the threat of terrorism, has a similar response model advisory—"Run, Hide, Tell".[9]

A higher value has been placed on providing security agencies with intelligence to improve efficiency and effectiveness of response. Hence, the "Fight" tactic in the US model has been modified to "Tell", similar to that in the Australian and Canadian systems. Considering the closer proximity of security agencies around Singapore, provision of intelligence either by calling SPF at 999, SMS 71999 if unable to speak, or submitting information via SGSecure app is emphasised. Specific silent communication mechanism through the SGSecure app has also been developed to allow informants (affected people of the armed attack in this scenario) to provide secured, silent messages to the response agencies directly.

The adapted model is useful in a setting where staff, patients and visitors can follow the steps of action, especially the "Run" component. However, in an ED or certain areas of the hospital such as intensive care unit, operating/procedure rooms and wards, there are patients who are not mobile or are physically impaired. Many patients are also bed-bound, on life-support equipment or undergoing procedures/surgery.[10]

Healthcare staff must always consider the well-being and safety of their patients and visitors first. During an armed assailant incident, the crisis may overshadow the need to prioritise their own safety. Hence, Inaba et al. suggested an alternate strategy of "Secure, Preserve, Fight" that can be adopted by the healthcare sector to address these concerns.[11]

- Secure: For the safety of patients who cannot be evacuated due to the aforementioned reasons, and also the staff who need to be with them, the location

should be promptly secured. Locking mechanism should be immediately activated by the respective areas to secure their entrances, so that the assailant is unable to enter those zones.

- Preserve: Healthcare staff taking care of these patients should continue providing ongoing care to preserve life.
- Fight: This strategy should be used only if absolutely necessary, as stated before.

However, for the Singapore context, it would be more appropriate to adapt the "Fight" component to the "Tell" tactic. Rarely, there may be a need to consider incapacitating the armed assailant in the event they are identified. But this should only be undertaken as a last resort to protect life.

Thus, based on this best available evidence and in line with the national initiative of SGSecure to counter terrorism, adopting the model of "Run, Hide, Tell" or "Secure, Preserve, Tell" is recommended. This needs to be individualised, taking into consideration the infrastructure, department and types of patients. Adopting strategies that would best suit Singapore's needs can significantly reduce the risks to patients and staff.

Healthcare workers (HCWs) in the proximity of the armed assailant should not attempt to engage the assailant in any way, whether verbal and/or physical. Trained security personnel can attempt to de-escalate the situation by maintaining adequate distance from the attacker and not try to apprehend or overpower the assailant. They can continue talking and engaging the assailant and buy time where possible.

Another key concept that needs to be a part of the response model is "Treat". Being in a healthcare setting, this is intuitive for any response. Once the scene is safe and the assailant has been neutralised, the priority is to identify seriously wounded casualties, patients or staff, who require immediate care for injuries. For someone who is bleeding profusely while hiding, all staff should be trained to identify and treat airway obstruction and major arterial haemorrhage by application of direct pressure or a tourniquet. Healthcare facilities should ensure they have adequate tourniquets to respond to an armed assailant incident.

Care provided during an armed assailant event should be remembered by the acronym THREAT:[12]

T – Threat suppression

H – Haemorrhage control

RE – Rapid Extrication to safety

A – Assessment by medical providers

T – Transport to definitive care

Management of public and media during the incident

In the current era of social media, news of an incident will travel fast, resulting in influx of media personnel, family and friends of patients and staff, as well as curious bystanders. Anticipating this, a pre-identified area some distance from the hospital should be cordoned off by the security to ensure public safety.

Arrival of law enforcement officers

When armed officers from the SPF or the Special Tactics and Rescue (STAR) team (a tactical unit of SPF) arrive, the security in-charge should quickly liaise with them at a designated meet-up point and brief them about the current details of the incident, precautionary actions taken, and review floor plans and CCTV images as necessary. Staff and visitors should remain calm and strictly follow the enforcement team's instructions. They should not ask the officers for help, leading to delay or impeding the latter's movement as their primary aim is to neutralise the threat. People should only exit the area when instructed to do so by the police or security officers. Upon neutralisation of the threat and after advice from SPF, an "All Clear" message should be broadcasted by security across the hospital.

Post-incident

Recovery and business continuity

Once the attack has ended and the threat has been neutralised, there is a need to assess the ability of the department or hospital to continue routine operations. Certain operations may be affected when that particular area is secured for investigation, or suffers damage to facilities and equipment. Those in charge must determine if the department retains the capacity and staff to treat its existing patients and new casualties, or an alternate treatment area at a different location needs to be set up to resume operations.

Behavioural health support plan

In the immediate aftermath of an attack, HCWs, patients and other witnesses may be "secondary victims" due to physical or mental trauma. As part of the recovery process, the hospital needs to consider providing rapid psychological assessment and first aid to the affected people as necessary. All HCWs from the affected areas should undergo a debriefing session from their supervisors before resuming work. Their particular needs or concerns should be appropriately addressed, with those affected provided support by peers or medical social workers. Such support, after the incident and also as outpatient follow-up, should be arranged for all

people affected by the event, to reduce the traumatic impact as well as to ease their recovery.

After-action review

A review should be conducted after an incident in a timely manner, as valuable insights can be obtained during this process. Improvement of response plan is the goal of any preparedness effort. If the response plan is modified, the new plan should be retested to assure that it improves the entire system's capability to respond.

Preparedness to an armed assailant attack

Every hospital should develop a response plan to effectively address this risk. Valuable input from internal and external stakeholders such as SPF, Singapore Civil Defence Force (SCDF), Certis Cisco security and Ministry of Health should be obtained while devising these plans. Familiarisation of the response plan, supplemented by periodic training of all healthcare staff, will play an important role in triggering an initial response, as well as adopting the subsequent appropriate steps to mount an effective and efficient response. The training module of the response plan, including videos, should be developed and made available on the organisation's intranet for periodic training.

The next step would be to conduct table-top as well as full-scale armed assailant mock drill involving healthcare staff and volunteers participating as an armed assailant and patients. Officers from SPF, SCDF and STAR teams should come to the hospital in full gear to respond to this mock event. These exercises are a great way to evaluate the preparedness plan, clarify roles and responsibilities, provide training, improve coordination between internal and external stakeholders, obtain participant feedback, and identify deficiencies and recommendations for plan improvement. The lessons learnt from these joint exercises would be invaluable to instil confidence and improve readiness for such incidents. Moreover, with advancement in technology, deployment of CCTV with real-time artificial intelligence video surveillance, facial recognition at entry points, and use of robots to help security scale up patrols without manpower resourcing can also be adopted for surveillance and deterrence of such attacks.

In summary, armed assailant events in the hospital are rare, and it is challenging to predict their occurrence. The emergency preparedness units of all hospitals should work together, along with various stakeholders, especially SPF and SCDF, to develop hospital-specific armed assailant incident response plan. Regular staff training, incorporating online learning modules and simulated drills, will increase the resilience and capability of hospitals to respond to a potential threat in the future. This would be of immense benefit to keep healthcare facilities safe, both for staff as well as for the community.

REFERENCES

1. US Department of Health and Human Services. Incorporating Active Shooter Planning into Health Care Facility Emergency Operations Plans, 2014. Available at: http://www.phe.gov/preparedness/planning/Documents/active-shooter-planning-eop2014.pdf. Accessed 12 June 2021.
2. Kelen GD, Catlett CL, Kubit JG, et al. Hospital-based shootings in the United States: 2000 to 2011. Ann Emerg Med 2012;60:790-8.
3. Goralnick E, Walls R. An active shooter in our hospital. Lancet 2015;385:1728.
4. Ministry of Home Affairs. Singapore Terrorism Threat Assessment Report 2021, 23 June 2021. Available at: https://www.mha.gov.sg/mediaroom/press-releases/singapore-terrorism-threat-assessment-report-2021/. Accessed on 15 July 2021.
5. Rorie S. Implementing an active shooter training program. AORN J 2015;101:C5-6.
6. Advanced Law Enforcement Rapid Response Training (ALERRT) Center at Texas State University. Avoid deny defend. Available at: https://www.avoiddenydefend.org/ Accessed on 12 June 2021.
7. Australia-New Zealand Counter-Terrorism Committee. Active Armed offender guidelines for crowded places, 2017. Available at: https://www.nationalsecurity.gov.au/Media-and-publications/Publications/Documents/active-armed-offender-guidelines-crowded-places.pdf. Accessed on 12 July 2021.
8. Ontario Hospital Association. Code Silver: Person with a weapon, 2019. Available at: https://www.oha.com/Documents/Code%20Silver%20Development%20Guidance.pdf. Accessed on 12 July 2021.
9. SGSecure. Available at: https://www.sgsecure.gov.sg/. Accessed on 12 July 2021
10. Gerold KB. Hospital Planning and Response to an Active Shooter Incident: Preparing for the n=1. Anesthesiol Clin 2019;37:161-9.
11. Inaba K, Eastman AL, Jacobs LM, et al. Active-shooter response at a health care facility. N Engl J Med 2018;379:583-6.
12. Healthcare & Public Health Sector Coordinating Council. Active shooter planning and response. International Association of Emergency Medical Services Chiefs, 2017.

LETTER TO THE EDITOR

Ann Acad Med Singap 2021;50:717-20
https://doi.org/10.47102/annals-acad medsg.2020453

Impact of COVID-19 on paediatric and OBGYN residency training in Singapore

Dear Editor,

The ongoing COVID-19 pandemic is likely to have far-reaching implications on residency training under the competency-based residency system, Accreditation Council for Graduate Medical Education I (ACGME-I). COVID-19 caused considerable disruption due to the longer infectious period and greater asymptomatic transmissibility.[1] This study aims to identify the impact of COVID-19 on paediatrics, and obstetrics and gynaecology (OBGYN) residency in KK Women's and Children's Hospital (KKH), Singapore.

A qualitative phenomenological approach was used to conduct semi-structured individual interviews involving 15 paediatrics and 15 OBGYN residents. These interviews were conducted either in person or via telecommunication platforms between March 2020 and April 2020. Residents were selectively sampled to ensure diversity in personal roles and social background such as parents, marriage status and years in residency (Table 1A). The conceptual framework of this study was structured with reference to the studies from previous pandemics.[2-7] Data saturation[8] was reached after a total of 30 residents, with 15 residents from each programme interviewed.

The interview guide consisted of a standardised set of open-ended questions focusing on the 3 major domains (Table 1B) derived from literature review of studies on SARS outbreak and H1N1 pandemic:[2-7] training, clinical environment and psychosocial impact. Thematic analysis was performed to identify emerging themes through descriptive phrases from the participants (Table 1C). To reduce potential bias, the interviews were recorded and each transcript was reviewed for themes by at least 2 authors independently, who were not involved in the interview process and were from the other residency programme.

From the transcripts of the interview, the participants described key aspects of their clinical training directly influenced by COVID-19 pandemic (Theme 1). With residents being redeployed to cover the isolation wards, rotations to subspecialties had been reduced. Non-urgent clinic visits and elective surgeries were rescheduled. Residents rotated to external hospitals were arranged to remain in these external postings, delaying the resumption of their core postings. Collectively, these had affected their year-on-year training progression. Residents were also unable to attend teaching sessions due to the insufficient manpower in the wards. A multitude of activities designed for learning were reduced, including grand ward rounds, clinical audit meetings, conferences, bedside tutorials, multidisciplinary team meetings, workshops and elective postings. Some of these courses are compulsory requirements for residency, hence their deferment would disrupt residency progression. Cancellation of exit examination has affected career progression, resulting in low morale among senior residents. The delivery of clinical education was challenging as didactic teachings were conducted over teleconferencing platforms such as Zoom. Virtual teaching may not be effective due to the lack of personalised contact and classroom participation. Moreover, videoconferencing was unable to replace practical hands-on training sessions. Thus, the quality of learning from clinical day-to-day work was perceived to have been significantly compromised. To practise social distancing, residents were no longer able to observe a senior colleague in a clinic session to learn specific counselling skills.

Changes in the clinical environment have significantly reduced the working efficacy of the residents (Theme 2). The hospital created a set of infection control protocols to provide guidance in suspect and confirmed cases' management. As these protocols were constantly evolving, it was challenging for residents to keep up. Respondents expressed the frustration of information overload as multiple emails on protocol updates were received regularly. The experience was aggravated with protocols that were unfamiliar in their normal daily practice. While personal protective equipment (PPE) and COVID-19 test kits provided safety assurance, donning PPE required additional time, especially during emergency situations such as acute resuscitation. Occasionally, strict protocols for PPE may not be stringently adhered to, raising concerns over the potential exposure to COVID-19. Additionally, the physician-patient relationship was often hampered by the usage of PPE as non-verbal communication, such as subtle cues during clinical interactions, was significantly impacted. Specifically, the fear that children experience when seeing healthcare staff in PPE greatly affected the clinical experience of the paediatrics residents, reducing

Table 1. Design of the study

(A) Profile of the residents, with baseline demographics and year of residency training

	OBGYN residency (n=15)	Paediatrics residency (n=15)
Demographics		
Age, years, mean±SD	31.8±3.6	31.5±3.0
Sex		
Male, no. (%)	3 (10.0)	7 (23.3)
Female, no. (%)	12 (40.0)	8 (26.7)
Nationality		
Singaporean, no. (%)	14 (46.7)	11 (36.7)
Others, no. (%)	1 (3.3)	4 (13.3)
Marital Status		
Single, no. (%)	8 (26.7)	8 (26.7)
Married, no. (%)	7 (23.3)	7 (23.3)
Year of residency training, no. (%)		
Year 1	1 (3.3)	3 (10.0)
Year 2	2 (6.7)	2 (6.7)
Year 3	2 (6.7)	2 (6.7)
Year 4	3 (10.0)	1 (3.3)
Year 5	2 (6.7)	4 (13.3)
Year 6	5 (16.7)	3 (10.0)

Percentage is that of total participants
OBGYN: obstetrics and gynaecology: SD: standard deviation

(B) Standardised set of interview questions

Interview Questions
Key questions
1. Can you share how things at the workplace are different now compared to peace time? How do you feel about these changes? (training/clinical environment)
2. Can you share how things in your personal life have changed since the start of the pandemic? How do you feel about these changes? (psychosocial)
3. What would you like the hospital and residency programme to do (or to do differently) for residents like yourself in this time?
Probing question examples (if specific research areas have not been covered in key questions):
1. How do you feel about having to work in a high-risk area?
2. How do you feel about the residency training that you are experiencing now?
3. How do you feel about the work assignments (e.g. rosters, job scope) that you are currently performing?

their work satisfaction. Decrease in the number of doctors participating in ward rounds also resulted in a lack of continuity of care. The issue of burnout has also been a major concern. With the greater division of manpower to cover both the general and isolation wards, the workload was significantly higher for each resident. Some respondents reported an increased number of overnight calls, sometimes up to 3 times in a week.

The impact of COVID-19 on the resident's psychosocial well-being may directly affect their performance

(C) Emerging themes through thematic analysis of the descriptive phrases from the participants

Impact of COVID-19 on three major themes	Collective concerns disclosed by participants
Theme #1: The pandemic has direct influence on the quantity and quality of clinical training	a) Quantity: Insufficient subspecialty training and skills training b) Quantity: Reduction or cancellation of courses, conferences, bedside tutorials, elective postings and exit examinations c) Quality: Although alternative ways of teaching were established, they may not be the most effective way to teach residents
Theme #2: The changes in the clinical learning environment to ensure clinician and patient safety create challenges in working efficiently and effectively	a) Constant changes in workflow can be confusing and challenging b) Residents feel safe in the new working environment c) Safety protocols indirectly affected the physician-patient relationship d) Diversion of manpower to isolation wards resulting in longer working hours/more calls
Theme #3: The impact of the pandemic on the residents' psychosocial well-being may directly affect their performance	a) Personal well-being of residents was affected b) A reduction in the interaction with family and friends due to concerns of transmission of COVID-19 c) Support from the senior management is important

(Theme 3). While most respondents felt empowered to contribute to society and the community at large, some experienced low morale and motivation due to leave cancellations, concern over residency promotion, repeated deployment for isolation ward shifts, and the impact on work-life balance. The residents expressed fears that this may lead to burnout and being underappreciated. There were also concerns of being stigmatised on being tested positive for COVID-19. Additionally, residents were concerned about possible transmission of the disease to their family members and friends, especially those with young children. To prevent the potential spread of COVID-19, residents had been refraining from meeting their friends and extended families. Some residents made care arrangements for their children to minimize the risk of exposure. While most family members were understanding and supportive, one respondent recounted that she was advised not to work in the high-risk area if given the choice. Lastly, respondents expressed concerns about the lack of information and transparency to their training continuity as well as work protocols. The issues of paucity of input from the residents, and lack of engagement in matters pertaining to changes in policies and rosters were raised. The residency programmes had not provided clarity or reassurances on the impact of changes in the training on their individual progression. Although the efforts of programme executives in gathering feedback and arranging alternative modes of teaching were appreciated, some respondents felt that motivation from the management would boost their morale.

There are limitations to this study. It is worth noting that KKH is a dedicated standalone women's and children's hospital that does not routinely provide adult emergency medicine or adult non-OBGYN service. Hence, it may not be experiencing the full impact of the COVID-19 pandemic compared to a general hospital. However, the perceptions of our residents may be extrapolated and generalisable to the residents of other specialties.[9,10] Further research is needed to determine the impact of these implemented measures on clinical training and resident wellness.

In conclusion, our residents have been significantly adversely affected by COVID-19 during the ACGME-I training. As the ACGME-I structure is highly time sensitive, residents preparing for exit examination are especially affected due to the magnitude and prolonged duration of the pandemic. Various interventions to minimise the impact should be considered early, such as the use of online learning platforms and exercising flexibility in promotion requirements. In addition, all hospitals should encourage a supportive work environment, and consult residents in the formulation of key protocols. These measures are crucial to ensure the physical and mental well-being of residents to prevent the effects of stress and burnout.

Acknowledgements

We would like to acknowledge Dr Victoria Chua, Ms Valencia Zhang, Ms Jamie Thea Jiaying Lin and Ms Choo Xin Hui for their contributions to the interview transcriptions. We would also like to acknowledge Ms Charlene Ong for her assistance in administrative matters and study coordination.

REFERENCES

1. Wilder-Smith A, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? Lancet Infect Dis 2020;20:e102-7.
2. Rambaldini G, Wilson K, Rath D, et al. The impact of severe acute respiratory syndrome on medical house staff: a qualitative study. J Gen Intern Med 2005;20:381-5.
3. Chong MY, Wang WC, Hsieh WC, et al. Psychological impact of severe acute respiratory syndrome on health workers in a tertiary hospital. Br J 2004;185:127-33.
4. Maunder R, Hunter J, Vincent L, et al. The immediate psychological and occupational impact of the 2003 SARS outbreak in a teaching hospital. CMAJ 2003;168:1245-51.
5. Brooks SK, Dunn R, Amlôt R, et al. Thematic review of social and occupational factors associated with psychological outcomes in healthcare employees during an infectious disease outbreak. J Occup Environ Med 2018;60:248-57.
6. Matsuishi K, Kawazoe A, Imai H, et al. Psychological impact of the pandemic (H1N1) 2009 on general hospital workers in Kobe. Psychiatry Clinical Neurosci 2012;66:353-60.
7. Sherbino J, Atzema C. "SARS-Ed": severe acute respiratory syndrome and the impact on medical education. Ann Emerg Med 2004;44:229-31.
8. Saunders B, Sim J, Jinks C, et al. Saturation in qualitative research: exploring its conceptualization and operationalization. Qual Quant 2018;52:1893-907.
9. Lai J, Ma S, Wang Y, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open 2020;3:e203976.
10. Seow J, Lin SX, Khor YP, et al. Stress and Strain in an Orthopaedic Department on the frontlines during the COVID-19 Pandemic: An Analysis of Burnout and the Factors Influencing It. Ann Acad Med Singap 2020;49:814-6.

Jason Lam Shang Leen [1]*MD*,
Tiffany Tuck Chin Wong [*2]*MBBS*, Chee Wai Ku [2] *MD*,
Janine Cynthia Koh [1]*MBBS*, Tu Anh Pham Nguyen [1]*MD*,
Raveen Shahdadpuri [1]*MRCPI*, Manisha Mathur [2]*MBBS*,
Cristelle Chow [1]*MBBS*

[1] Department of Paediatrics, KK Women's and Children's' Hospital, Singapore
[2] Department of Obstetrics and Gynecology, KK Women's and Children's Hospital, Singapore
[*] Primary co-author

Correspondence: Dr Jason Lam Shang Leen, KK Women's and Children's Hospital, 100 Bukit Timah Rd, Singapore 229899.
Email: jason.lam@mohh.com.sg

LETTER TO THE EDITOR

Ann Acad Med Singap 2021;50:721-3
https://doi.org/10.47102/annals-acadmedsg.2021214

Preparing for caesarean delivery from the eyes of expectant mothers and their partners: A questionnaire study

Dear Editor,

As the rate of caesarean delivery climbs, optimising its outcomes has become a topic of increasing relevance to clinical practice. Negative birth experiences are associated with lower quality of life and traumatic stress symptoms.[1] It is therefore important to evaluate and enhance patient-centric outcomes such as overall satisfaction, in addition to clinical outcomes. A secondary study involving more than 6,000 women found that caesarean delivery itself is a significant predictor of a negative birth experience.[1] Conversely, smaller primary comparative studies have reported significantly higher satisfaction and fulfilment,[2] as well as lower anxiety and guilt scores[3] among women who underwent planned caesarean delivery compared with women who delivered vaginally. The contrast in results is not surprising given that the experience is influenced by many factors. The findings of partners' experiences, moreover, raise concern. A systematic review of fathers' experiences found that healthcare systems tend to situate fathers in an ambivalent space, as neither patient nor visitor, diverging from their desire to be engaged and supportive in the pregnancy journey.[4]

Notably, there is an absence of published data on paired patients' and partners' caesarean delivery experience in our population.

To address this gap, we designed a questionnaire study among a random sample of approximately 100 couples at KK Women's and Children's Hospital, Singapore. Women and their partners above 21 years of age who had an elective caesarean delivery of a live infant and who were able to read English were invited to join the study. The primary aim was to elucidate couples' experience of preparing for delivery and to evaluate the adequacy of information provided. Secondary aims were to elucidate sources of information accessed and perceptions of their usefulness; distil valued elements in the pregnancy journey; and obtain suggestions for improvement. The questionnaire comprised separate sections for women and their partners with multiple-choice, Likert scale and open-ended questions to obtain quantitative and qualitative data. A pilot study of 20 couples was conducted to establish face validity and user friendliness of the questions.

A total of 111 couples were approached during the study period. Of this, 85 (77%) responses were received. The majority (73/85, 86%) included responses from both women and their partners. Two-thirds of women had one or more previous caesarean sections (54/85, 64%), while the remaining had a primary caesarean section (31/85, 36%). Three-quarters of partners (54/75, 74%) had accompanied the woman during most or all clinic visits, antenatal classes and hospital admissions.

With regard to the preferred mode of delivery (prior to visiting the obstetrician), responses were divided between caesarean section (24/85, 28%), normal vaginal delivery (30/85, 35%) and no preference (31/85, 36%). The point at which the eventual decision for caesarean section was made ranged from less than 1 week (20/84, 24%) to more than 3 months prior to delivery (23/84, 27%). Among the former, the most common patient-reported indications for caesarean delivery were a combination of obstetric factors (e.g. poorly controlled maternal medical conditions, placenta previa and multiple gestations) (5/20, 25%), 1 or more previous caesarean section(s) (4/20, 20%) and macrosomia (4/20, 20%). On the follow-up question of preparedness, a minority of women (5/82 6%) felt they did not have enough time to think about and prepare for delivery.

As studies have demonstrated an association between unplanned caesarean delivery and a negative birth experience,[5,6] the discussion on the mode of delivery should ideally be initiated early, or at least when the possibility of caesarean delivery arises, even if the final decision is made later. There may still be instances when this is not possible due to unexpected factors. Greater sensitivity, attention and support are key in these instances.

Of the plethora of information sources, doctors were the most accessed (69/85, 81%) and useful (26 out of 47 responses, 55%) source of information. The latter held true among both "graduate mothers" (university/college graduates) (12 out of 19 responses, 63%) and "non-graduate mothers" (14 out of 28 responses, 50%). Majority of women also reported that the information provided by healthcare professionals was adequate (65/85, 76%) and understood by them (74/85,

87%). Qualitative data revealed that women viewed information provided by doctors as reliable and they valued doctors' professional experience.

This reflects the profound degree of trust in the obstetrician-patient relationship in our population. This is similar to the findings of other studies that concluded that healthcare providers are a frequently accessed[7,8] and valued[9] source of information. In fact, a survey among over 600 women who used the internet as a source for pregnancy-related information found that prior to seeking information online, almost 70% of women sought information from healthcare providers.[10]

In terms of discussion on the various aspects of delivery, most women could remember the risks of surgery to themselves (67/85, 79%) and discussion on types of anaesthesia during surgery (56/85, 66%), while fewer could remember being told what to expect in the post-partum unit (25/85, 29%) and what to expect about the recovery process (41/85, 48%). There was no statistical difference in overall scoring between women who underwent primary caesarean section and those who underwent repeat caesarean section (P=0.67). As explaining risks has more overt medico-legal consequences if omitted, obstetricians may be focused on this aspect. Anxious mothers themselves may also be focused on obtaining and understanding information on the surgery itself as opposed to what to expect after. To address this disparity, we propose that the process of information-sharing be enriched by technology. In this study, the internet and/or social media was the second most commonly accessed (60/85, 71%) and useful (9 out of 47 responses, 19%) source of information. Qualitative data revealed that favourable aspects were round-the-clock accessibility, pictorial representation and reliability of hospital websites. Hence, offering patient education resources on a hospital-based website or application by leveraging audiovisual tools could complement discussions in the clinic.

Thematic analysis revealed that the best part of couples' experience was childbirth itself, and feeling supported by their partners and the healthcare team in the process (Table 1). Majority of the couples indicated "strongly agree or agree" to having the opportunity to ask questions (women: 76/85, 89%; partners: 60/73, 82%), feeling involved in the process of planning and preparing for delivery (women: 68/85, 80%; partners: 59/73, 81%) and knowing what to expect on the day of

Table 1. Thematic analysis of women's and their partners' responses to the question on the best and worst part of their experience

Looking back, what was the best part of your experience?		
	Patients (n=85), no. (%)	**Partners (n=73), no. (%)**
Support from the healthcare team	37 (44) Themes included: feeling cared for, seeing the baby being taken care of, receiving prompt help, positive staff attributes.	24 (33) Themes included: seeing the woman and baby being taken care of, follow-up by doctors and nurses after delivery, receiving prompt help, caring and friendly environment.
Childbirth experience and support from the partner	23 (27) Themes included: seeing the baby being born safely, hearing the baby cry, skin-to-skin contact with the baby, having the partner present during delivery.	27 (37) Themes included: witnessing delivery of the baby, knowing that the woman and baby are safe, being with the woman during delivery, being a father.
Looking back, what was the worst part of your experience?		
	Patients (n=85), no. (%)	**Partners (n=73), no. (%)**
Antepartum	13 (15) Themes included: visiting multiple different clinics, long waiting times for consultation.	6 (8) Themes included: long waiting times for consultation, having to leave a call-back request when calling the telephone operator.
Peripartum	13 (15) Themes included: feeling nervous, partner not being permitted within the operating theatre, receiving the epidural and medications, complications during delivery.	19 (26) Themes included: waiting time between admission and delivery, waiting outside the operating theatre, complications during delivery.
Postpartum	21 (25) Themes included: post-procedure tiredness and pain, security entry for carers and guests.	13 (18) Themes included: seeing the woman in pain and tired after the delivery, language barrier with staff.

delivery (women: 62/85, 73%; partners: 58/73, 79%). Most women also reported that the process of listing for caesarean delivery was smooth (64/85, 75%) and described staff on the day of surgery positively (79/85, 93%), with the following descriptors most commonly used: helpful (59/85, 69%), patient (23/85, 27%), and experienced/professional (12/85, 14%).

Almost half of women (38/85, 45%) and partners (35/73, 48%) did not report any negative experience, suggesting they had an overall positive experience. Of those who reported negative experiences, issues related to processes and logistics formed the common thread across the pregnancy journey (Table 1). This emphasises the importance of adopting systems-based style of practice. While it takes time to implement modifications to workflows or services, the healthcare team plays an integral role in pre-empting experiences or moderating patient expectations. These may be a result of obstetric factors (e.g. requiring more frequent and multidisciplinary appointments for monitoring of medical conditions in pregnancy) or system factors (e.g. postponement of elective procedures due to emergent procedures).

In conclusion, the findings of this study are a reminder for clinicians to celebrate the extraordinary experience of pregnancy and birth with each couple. We have proposed recommendations for improvement, which hopefully will keep couples at the heart of our service.

Acknowledgements

We would like to thank the postpartum ward nursing team at KK Women's and Children's Hospital for their kind assistance with recruitment.

REFERENCES

1. Smarandache A, Kim TH, Bohr Y, et al. Predictors of a negative labour and birth experience based on a national survey of Canadian women. BMC Pregnancy Childbirth 2016;16:1-9.
2. Blomquist JL, Quiroz LH, MacMillan D, et al. Mothers' satisfaction with planned vaginal and planned cesarean birth. Am J Perinatol 2011;28:383-8.
3. Wiklund I, Edman G, Larsson C, et al. First-time mothers and changes in personality in relation to mode of delivery. J Adv Nurs 2009;65:1636-44.
4. Steen M, Downe S, Bamford N, et al. Not-patient and not-visitor: a metasynthesis fathers' encounters with pregnancy, birth and maternity care. Midwifery 2012;28:422-31.
5. Rijnders M, Baston H, Schönbeck Y, et al. Perinatal factors related to negative or positive recall of birth experience in women 3 years postpartum in the Netherlands. Birth 2008;35:107-16.
6. Waldenström U, Hildingsson I, Rubertsson C, et al. A negative birth experience: prevalence and risk factors in a national sample. Birth 2004;31:17-27.
7. Puia DM. The cesarean decision survey. J Perinat Educ. 2013; 22:212-25.
8. Kolip P, Büchter R. Involvement of first-time mothers with different levels of education in the decision-making for their delivery by a planned Caesarean section. Women's satisfaction with information given by gynaecologists and midwives. J Public Health 2009; 17:273-80.
9. Declercq ER, Sakala C, Corry MP, et al. Major survey findings of listening to Mothers SM III: New mothers speak out: Report of National Surveys of Women's Childbearing Experiences Conducted October-December 2012 and January-April 2013. J Perinat Educ 2014;23:17-24.
10. Lagan BM, Sinclair M, George Kernohan W. Internet use in pregnancy informs women's decision making: a web-based survey. Birth 2010;37:106-15.

Lavisha S Punjabi [1]*MBBS*, Lional Karunamary [2]*MRCOG*, Shephali Tagore [2]*FRCOG*, Manisha Mathur [1]*FRCOG*

[1] Department of Obstetrics and Gynaecology, KK Women's and Children's Hospital, Singapore
[2] Department of Maternal and Fetal Medicine, KK Women's and Children's Hospital, Singapore

Correspondence: Dr Manisha Mathur, Department of Obstetrics and Gynaecology, KK Women's and Children's Hospital, 100 Bukit Timah Rd, Singapore 229899.
Email: manisha.mathur@singhealth.com.sg

LETTER TO THE EDITOR

Ann Acad Med Singap 2021;50:724-8
https://doi.org/10.47102/annals-acadmedsg.2021228

Non-tuberculous mycobacteria infections in peritoneal dialysis: Lessons from a 16-year single-centre experience

Dear Editor,

Non-tuberculous mycobacteria (NTM) infections in peritoneal dialysis (PD) patients are uncommon, but they have been increasingly recognised as causes of morbidity. NTM are generally non-pathogenic, but given their abundance in the environment, they pose a threat to PD patients who have broken integument, indwelling devices and relative defects in cell-mediated immunity.[1]

The growth of NTM is enhanced in warmer climates, which is common in tropical Asian countries. NTM are classified as rapid or slow growing, defined by their capacity to form visible colonies before or after 7 days of subculture. Most NTM infections reported in the literature were of rapidly growing species.[2] Despite the rapid growth of NTM, it still takes 3–7 days to culture them. This delays diagnosis, which is often further delayed due to a low index of suspicion, with misdiagnosis as culture-negative PD infections. The treatment of NTM infections is challenging; PD patients with NTM infections have been reported to do poorly.[2-5] Rates of PD catheter loss and change of dialysis modality are high. Encapsulating peritoneal sclerosis (EPS) is a late complication from NTM with significant mortality.[3,4,6] In this study, we describe the clinical outcomes of PD-associated NTM infections in National University Hospital PD Unit and propose treatment strategies.

As a follow-up to an earlier series from our centre,[3] a retrospective study of all NTM infections in our PD programme from January 2011 to May 2020 was conducted. Data collected included demographics, diagnosis method, treatment regimen, and patient outcomes including catheter loss, switch of dialysis modality and mortality. Ethics approval was obtained from our institutional review board (reference number 2020/00662).

There were 18 patients with NTM infections during our study period: 4 peritonitis cases, 10 exit site infections (ESI), and 4 concomitant ESI with peritonitis. *Mycobacterium abscessus* accounted for 89% of infections. The patient population was multiethnic, with a median age of 53 years and a median dialysis vintage of 2 years. Diabetes mellitus was the commonest cause of end-stage kidney disease. The median time from presentation to diagnosis of NTM infection was 6 days (range 2–35 days). All patients were treated with combination antibiotics in consultation with an infectious disease specialist. Eighty-nine percent of patients received amikacin and 78% received clarithromycin, with a median treatment duration of 5 months. PD catheter was removed in 17 of 18 patients and all 4 patients who did not undergo early catheter removal eventually developed recurrence, requiring removal 1.5–2 years after the first diagnosis of NTM infection. Three of 18 patients had a new PD catheter reinserted at a different site shortly after removal of the infected catheter (Table 1).

To the best of our knowledge, this is the largest single-centre case series of PD-associated NTM infection reported for Asia and internationally. PD-associated NTM peritonitis was first described in 1983 by Pulliam et al. with 100% mortality.[7] More reports of PD-associated NTM infections have since emerged.[3,4] Early diagnosis at the ESI stage instead of the peritonitis stage may improve outcomes. However, this is challenging, as initial presentation and PD effluent findings are often indistinguishable from bacterial infections. Furthermore, acid-fast bacillus (AFB) smear-negative disease is common.[5] Only 2 of the 10 patients with ESI in our study had positive AFB smears of the exit site discharge. A high index of suspicion and early testing for AFB is required to avoid the sequelae of late diagnosis. If initial gram stain and bacteria culture are negative, or response to first-line antibiotics is poor, mycobacterial and fungal investigation should be conducted.[2] We recommend repeat AFB smears especially if the exit site discharge is mucoid, sticky or greyish. *M. abscessus* accounted for the majority of cases in our series, similar to previous Singapore data collected.[3,8] In contrast, *M. fortuitum* and *M. chelonae* are more prevalent in other countries.[5] It is important to identify the causative NTM species because susceptibility to antimicrobials is often highly species-specific.[5] For *M. abscessus*, subspecies identification, if available, may be additionally helpful.[9]

PD-associated NTM infections are difficult to eradicate and invariably lead to high rates of catheter loss.[3-5] Prolonged antimicrobial use exposes patients to risks of complications such as ototoxicity and hepatitis.[3] Treatment failure is also an issue—in a series of 12 patients, 11 required prescription change to second-line antibiotics, while a further 5 patients needed third-line antibiotics due to poor response.[4] Our experience

Table 1. Comparison of treatments and outcomes in peritoneal dialysis patients with non-tuberculous mycobacteria infections from 2 case series

	No.	Age, years/ Sex	Catheter removal	Time from diagnosis to catheter removal	NTM infection recurrence	*Mycobacterium* species and antibiotic susceptibility Sensitive [S] Resistant [R]	Antibiotic therapy and duration	Technique failure (conversion to permanent HD)	3-month mortality	Adverse drug reaction
Current case series	1	68/M	Yes	2 days	No	*M. abscessus* [S] A, K, Cef, Clo, Cip	A, K, Clo 1 month	Yes	No	
	2	44/M	Yes	2 days	No	*M. fortuitum* [S] A, Cef, Cip [R] K	A, Cip 3 months	Yes	No	
	3	66/M	Yes	3 months	No	*M. abscessus* [S] A, K, Cef, Clo, Cip	A, Cef 1 month K 1 year	Yes	No	
	4	56/M	Yes	1.5 years	Yes	*M. fortuitum* [S] A, Cef, Clo, Cip [R] K	A, K 9 months Peritonitis relapse; K, Clo 9 months	Yes	No	Ototoxicity
	5	63/F	Yes	2 years	Yes	*M. abscessus* [S] A, K, Cef, Clo, Cip	A, K 5 months Peritonitis relapse; K, Clo 6 months	Yes	No	
	6	63/M	Yes	1 day	No	*M. neonarum* [S] A, K, Cef, Cip, Dox, Lev	A, Lev, Dox 1.5 months	Yes	No	
	7	43/F	Yes	3 days	No	*M. abscessus* [S] A, K, Cef [R] Cip	A 1 month K 9 months	No (HD 1 year then PD)	No	
	8	64/M	Yes	4 days	No	*M. abscessus* [S] A, K, Cef	A, Cef 3 months	Yes	No	
	9	63/M	No	NA	No	*M. abscessus* [S] A, K, Cef [R] Cip	K, Cip, Met 2 weeks	No	No	
	10	58/M	Yes	4 days	No	*M. abscessus* [S] A, K, Cef [R] Cip	A 2 months K 6 months	Yes	No	

Table 1. Comparison of treatments and outcomes in peritoneal dialysis patients with non-tuberculous mycobacteria infections from 2 case series (Cont'd)

	No.	Age, years/ Sex	Catheter removal	Time from diagnosis to catheter removal	NTM infection recurrence	*Mycobacterium* species and antibiotic susceptibility Sensitive [S] Resistant [R]	Antibiotic therapy and duration	Technique failure (conversion to permanent HD)	3-month mortality	Adverse drug reaction
Current case series	11	29/M	Yes	2 years	Yes	*M. abscessus* [S] A, K, Cef [R] Cip	A, K 2 months Peritonitis relapse; A 2 months K 6 months	Yes	No	
	12	64/F	Yes	2 years	Yes	*M. abscessus* [S] A, K, Cef [R] Cip	A, K, Clo 2 months ESI relapse; A 2 months K, Clo 7 months	No	No	
	13	67/F	Yes	8 days	No	*M. abscessus* [S] A, K, Cef [R] Cip	A, K, Cef 4 months	No (simultaneous PD catheter removal and insertion)	No	
	14	58/M	Yes	1 day	No	*M. abscessus* [S] A, K, Cef [R] Cip	A 1 month K, Clo 6 months	Yes	No	
	15	53/M	Yes	16 days	No	*M. abscessus* [S] A, K, Cef [R] Cip	A 1.5 months K, Clo 6 months	No (HD 3 weeks then PD)	No	
	16	54/M	Yes	4 months	No	*M. abscessus* [S] A, Lin [R] K, Cef	A, K, Cip, Lin 4 months	No (HD 6 months then PD)	No	Ototoxicity
	17	75/F	Yes	8 days	No	*M. abscessus* [S] A, K, Cef [R] Cip	A, K, Cef 5 months	Yes	No	Ototoxicity
	18	31/F	Yes	10 days	No	*M. abscessus* [S] A, K, Cef	A, K 6 months	Yes	No	

Table 1. Comparison of treatments and outcomes in peritoneal dialysis patients with non-tuberculous mycobacteria infections from 2 case series (Cont'd)

	No.	Age, years/ Sex	Catheter removal	Time from diagnosis to catheter removal	NTM infection recurrence	*Mycobacterium* species and antibiotic susceptibility Sensitive [S] Resistant [R]	Antibiotic therapy and duration	Technique failure (conversion to permanent HD)	3-month mortality	Adverse drug reaction
Case series by Renaud et al., 2011	1	58/M	Yes	5 days		*M. chelonae* Pansensitive	K, Cip 6 weeks	No (HD 6 months then PD)	No	
	2	63/M	Yes	9 days		*M. abscessus* [S] A, K	K 6 weeks	Yes	No	
	3	81/M	No	NA		*M. abscessus* Pansensitive	No	NA (death)	Yes (sepsis)	
	4	78/F	No	NA		*M. fortuitum* Pansensitive	A, Cip 3 months	NA (death)	Yes (cancer)	
	5	56/F	No	NA		*M. fortuitum* [S] A, K	No	NA (death)	Yes (sepsis)	
	6	70/M	Yes	NA		*M. abscessus* [S] A, K, Lin	A, K, Mero 1 month	Yes	Yes (AMI)	
	7	50/M	Yes	5 days		*M. abscessus* Pansensitive	K, Cip 3 months	Yes	No	
	8	56/M	Yes	1 month		*M. abscessus* [S] A, K	A, K 1 month	Yes	Yes (sepsis)	Hepatitis
	9	69/F	Yes	1 month		M. abscessus [S] A, K	K 6 weeks	No (HD 6 weeks then PD)	No	Psychosis
	10	60/M	Yes	6 days		*M. abscessus* [S] A, K	A, K 3 months	No (HD 3 months then PD)	No	Deafness

A: amikacin; AMI: acute myocardial infarction; Cef: cefoxitin; Cip: ciprofloxacin; Clo: clofazimine; Dox, doxycycline; F: female; HD: haemodialysis; K: clarithromycin; Lev: levofloxacin; Lin: linezolid; M: male; Mero: meropenem; Met: metronidazole; NA: not available; NTM: non-tuberculous mycobacteria; PD: peritoneal dialysis; [R] resistant; [S] sensitive

showed that conservative management, even with prolonged antimicrobials, resulted in poor outcomes and adverse effects. Three cases (Cases 4, 16 and 17) suffered permanent hearing loss from prolonged aminoglycoside use despite therapeutic drug monitoring. In contrast, Cases 13 and 15 were eradicated of NTM and remained on PD without recurrence after early removal of the catheter with reinsertion at a different site. Our centre has previously published a case series of 10 patients with PD-associated NTM infections from 2004–2009;[3] all patients suffered technique failure with none returning to PD. The 3-month mortality was higher in that series.

Table 1 outlines the treatments and outcomes in our case series in comparison with that of Renaud et al.[3] Both series proved the high rates of catheter loss and technique failure. Importantly, our series demonstrated 3 key points, the first being the futility of conservative management with catheter preservation and prolonged antimicrobials. Secondly, recurrence-free return to PD was achieved in 28% of patients with isolated ESI through diagnosis, catheter removal, appropriate antibiotics use and PD catheter reinsertion, either early on (Case 13), or at an appropriate time later (Cases 7, 9, 15, 16). No patient with NTM peritonitis returned to PD. NTM peritonitis did not recur in patients after conversion to haemodialysis, suggesting that effective antibiotics may prevent dissemination of NTM peritonitis. Thirdly, recurrence-free continuation of PD without conversion to haemodialysis is possible for patients with isolated ESI, with removal of the infected catheter and simultaneous reinsertion at a different site (Case 13); however, we caution that further study is required to define the patient selection criteria for this option.

Adjunct surgical techniques such as local thermal therapy and catheter deroofing have been found to be successful to prevent NTM peritonitis in Japan.[10] However, these techniques are operator dependent, and the species involved were mainly *M. chelonae* and *M. fortuitum*. It is unclear how effective these techniques would be for *M. abscessus*.

In conclusion, PD-associated NTM infections are associated with high morbidity, are very difficult to eradicate, and prolonged antimicrobials alone without catheter removal are associated with high recurrence, catheter loss and a significant risk of adverse effects. NTM infections require a high index of suspicion for diagnosis, and outcomes may be better with early recognition and prompt catheter removal. Early staged, or simultaneous catheter reinsertion is possible, and may allow patients to remain on PD if residual kidney function is adequate. There is a pressing need for better diagnostics and therapeutics to improve outcomes in infections.

Acknowledgements

The authors wish to thank all members of the peritoneal dialysis unit at National University Hospital for their contribution to NTM patient care.

REFERENCES

1. Holmes C, Lewis S. Host defense mechanisms in the peritoneal cavity of continuous ambulatory peritoneal dialysis patients. 2. Humoral defenses. Perit Dial Int 1991;11:112-7.
2. Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. [published correction appears in Perit Dial Int 2018;38:313]. Perit Dial Int 2016;36: 481-508.
3. Renaud CJ, Subramanian S, Tambyah PA, et al. The clinical course of rapidly growing nontuberculous mycobacterial peritoneal dialysis infections in Asians: A case series and literature review. Nephrology (Carlton) 2011;16:174-9.
4. Jiang SH, Roberts DM, Clayton PA, et al. Non-tuberculous mycobacterial PD peritonitis in Australia. Int Urol Nephrol 2013;45:1423-8.
5. Song Y, Wu J, Yan H, et al. Peritoneal dialysis-associated nontuberculous mycobacterium peritonitis: a systematic review of reported cases. Nephrol Dial Transplant 2012;27:1639-44.
6. Ono E, Uchino E, Mori KP, et al. Peritonitis due to Mycobacterium abscessus in peritoneal dialysis patients: case presentation and mini-review. Ren Replace Ther 2018;4:52.
7. Pulliam JP, Vernon DD, Alexander SR, et al. Nontuberculous mycobacterial peritonitis associated with continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1983;2:610-4.
8. Lim AYH, Chotirmall SH, Fok ETK, et al. Profiling non-tuberculous mycobacteria in an Asian setting: characteristics and clinical outcomes of hospitalized patients in Singapore. BMC Pulm Med 2018;18:85.
9. Jeong SH, Kim SY, Huh HJ, et al. Mycobacteriological characteristics and treatment outcomes in extrapulmonary Mycobacterium abscessus complex infections. Int J Infect Dis 2017;60:49-56.
10. Jo A, Ishibashi Y, Hirohama D, et al. Early surgical intervention may prevent peritonitis in cases with Tenckhoff catheter infection by nontuberculous mycobacterium. Perit Dial Int 2012;32:227-9.

Zi Yun Chang [1]*MBBS*, Pei Loo Tok [1]*MBBS*,
Boon Wee Teo [1,2]*MB BCh*, Weizhen Hong [1]*MBBS*,
Paul Anantharajah Tambyah [2,3]*MD*,
Martin Beng-Huat Lee [1]*PhD*

[1] Division of Nephrology, Department of Medicine, National University Hospital, Singapore
[2] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3] Division of Infectious Diseases, Department of Medicine, National University Hospital, Singapore

Correspondence: Dr Zi Yun Chang, Division of Nephrology, Department of Medicine, National University Hospital, NUHS Tower Block Level 10, 1E Kent Ridge Road, Singapore 119228.
Email: zi_yun_chang@nuhs.edu.sg

LETTER TO THE EDITOR

Ann Acad Med Singap 2021;50:729-32
https://doi.org/10.47102/annals-acad medsg.202146

A survey of young ophthalmologists' perception of training in Asia during COVID-19

Dear Editor,

The outbreak of the coronavirus disease 2019 (COVID-19) has resulted in the need to increase ward and critical care capacity, leading to temporary suspension of elective ophthalmic surgeries worldwide.[1] There has been significant reduction in outpatient activity and postponement of ophthalmology-based examinations.[2] Many trainees have been redeployed elsewhere. Ophthalmology congresses have been cancelled or converted to webinars, while residency teaching has been reduced or moved to virtual platforms where possible. These measures have mitigated the impact on residency training but cannot substitute the experience in clinics and time in the operating theatre. Prior plans made, such as fellowship training, may be postponed or cancelled, hindering career progression.

Young ophthalmologists (YOs) are trainees and early career ophthalmologists within the first 5 years of independent practice. The implications of the pandemic for training and career are expected to differ. We conducted a survey to determine how training for YOs have been affected by the pandemic in various countries and territories (Singapore, Malaysia, Taiwan, Hong Kong and India), between 6 May 2020 and 16 June 2020. It was adapted from the North West School of Surgery COVID-19 Training Disruption Notification Form[3] and Impact of the COVID-19 pandemic on urology residency training in Italy.[4] All respondents responded to all questions in the survey.

A total of 242 responses were obtained (response rate of 69.3%). Distribution was equal in sex (50.8% men) and training year (51.2% trainees). There was no significant difference in COVID-19 duties involvement. In total, 52 (21.5%) of the total respondents were involved in COVID-19 duties outside of routine ophthalmological practice, of whom 9 out of 52 (17.3%) were involved daily, while 43 (82.7%) were involved more than once a week. Of the 52 respondents, 25 (48.1%) were deployed out of their primary institution.

The current COVID-19 pandemic has seen examination postponement or cancellation affecting 52% of trainees (P<0.001). There were 22 ophthalmologists who had their fellowship plans delayed (P=0.027). There was a significant impact on YO training in multiple domains that have affected trainees disproportionately more than early-career ophthalmologists.

Table 1 shows areas where ophthalmological training were affected. Cancellation of teaching sessions have significantly affected trainees more than ophthalmologists, of which Singapore had the highest overall rate of cancellation, followed by Hong Kong (P<0.001).

More acute cases were reviewed in Singapore (38.1%) compared to Hong Kong (13.2%). Conjunctivitis is one of the most common ocular conditions diagnosed in the emergency department.[5] In Hong Kong,[6] those with acute conjunctivitis had their appointments postponed for at least 14 days. By then, a large proportion of the self-limited cases would have been resolved.[7]

YOs were redeployed from ophthalmology-related duties to critical care, emergency department, COVID-19 wards and screening facilities, worker dormitories and other locations. In view of outbreak in the worker dormitories, Singapore had the greatest change in clinical placement and this could affect residency training. Both ophthalmologists and trainees were affected by leave cancellations. Cancellation of training leave/conference leave was lowest in India. In fact, during the lockdown phase in India, 85.2% of respondents reported an increased frequency of attending webinars, with almost half attending more than 10 webinars on different disciplines.[8]

Additionally, 14 YOs returned to work earlier from their hospitalisation or non-acute illness medical leave. Staffing issue is prevalent worldwide amid the pandemic, and healthcare workers are stepping up voluntarily during times of need. However, it is worrying that some with symptoms of acute respiratory infection may feel pressured to return to work sooner than recommended. There may be a need for advocacy groups to increase awareness of the dangers of this culture to patients, YOs and affiliated healthcare workers.

Our survey has shown that almost all YOs have decreased exposure to surgical cases and 50–60% had practically complete suppression. Outpatient procedures such as intravitreal injections and laser procedures have seen substantial reduction. In all the countries and territories surveyed, surgical volume was reduced during the pandemic and restricted to urgent or emergent conditions.[9] A survey done by Rohan et al.[10] highlighted cataract surgery as ophthalmic trainees' biggest concern during the pandemic, especially for those who were starting.

Table 1. Number of ophthalmologists and trainees affected by COVID-19 pandemic in each country/territory for different areas of ophthalmology training and practice

	Total affected, no. (%)	Ophthalmologists affected, no. (%)	Trainees affected, no. (%)	*P* value
Cancellation of teaching sessions	116 (48.3)	47 (40.2)	69 (56.1)	0.014
Hong Kong	15 (65.2)			<0.001
India	26 (37.7)			
Malaysia	28 (60.9)			
Singapore	28 (66.7)			
Taiwan	19 (31.7)			
Cancellation/Postponement of examinations	94 (39.2)	30 (25.6)	64 (52.0)	<0.001
Hong Kong	8 (34.8)			0.513
India	29 (42.0)			
Malaysia	22 (47.8)			
Singapore	20 (47.6)			
Taiwan	15 (25.0)			
Change in clinical placement	78 (32.5)	28 (23.9)	50 (40.7)	0.006
Hong Kong	7 (30.4)			<0.001
India	17 (24.6)			
Malaysia	10 (21.7)			
Singapore	27 (64.3)			
Taiwan	17 (28.3)			
Cancellation/Postponement of fellowship plans	33 (13.8)	22 (18.8)	11 (8.9)	0.027
Hong Kong	3 (13.0)			0.027
India	12 (17.4)			
Malaysia	10 (21.7)			
Singapore	7 (16.7)			
Taiwan	1 (1.7)			
Cancellation of training leave	39 (16.3)	14 (12.0)	25 (20.3)	0.079
Hong Kong	8 (34.8)			0.004
India	7 (10.1)			
Malaysia	7 (15.2)			
Singapore	12 (28.6)			
Taiwan	5 (8.3)			
Cancellation of conference leave	74 (30.8)	38 (32.5)	36 (29.3)	0.590
Hong Kong	11 (47.8)			0.001
India	9 (13.0)			
Malaysia	14 (30.4)			
Singapore	19 (45.2)			
Taiwan	21 (35.0)			
Cancellation of annual leave	76 (31.7)	38 (32.5)	38 (30.9)	0.792
Hong Kong	6 (26.1)			<0.001
India	10 (14.5)			
Malaysia	19 (41.3)			
Singapore	23 (54.8)			
Taiwan	18 (30.0)			
Early return from hospitalisation leave/ non-acute illness medical leave	14 (5.8)	9 (7.7)	5 (4.1)	0.231
Hong Kong	1 (4.3)			0.054
India	3 (4.3)			
Malaysia	2 (4.3)			
Singapore	0			
Taiwan	8 (13.3)			

Table 1. Number of ophthalmologists and trainees affected by COVID-19 pandemic in each country/territory for different areas of ophthalmology training and practice (Cont'd)

	Total affected, no. (%)	Ophthalmologists affected, no. (%)	Trainees affected, no. (%)	*P* value
Reviewing more cases that present acutely i.e. emergency/walk-ins	49 (20.4)	15 (12.8)	34 (27.6)	0.004
Hong Kong	3 (13.2)			0.009
India	16 (23.2)			
Malaysia	8 (17.4)			
Singapore	16 (38.1)			
Taiwan	6 (10.0)			
Routine involvement in overnight call duties prior to COVID-19				
Yes	160 (66.7)			
No	80 (33.3)			
Decrease in call duty since COVID-19 onset	52 (21.7)			
Decrease %				
0–40	30 (57.7)			
41–80	18 (34.6)			
81–100	4 (7.7)			
Increase in call duty since COVID-19 onset	23 (9.6)			
Increase %				
0–40	17 (73.9)			
41–80	5 (21.7)			
81–100	1 (4.3)			
Similar or not applicable	165 (68.8)			
Decreased involvement in outpatient visits	196 (81.7)			
Decrease %				
0–40	83 (42.3)			
41–80	87 (44.4)			
81–100	26 (13.3)			
Decreased involvement in surgical cataract operations	217 (90.4)			
Decrease %				
0–40	31 (18.9)			
41–80	43 (19.8)			
81–100	133 (61.3)			
Decreased involvement in surgical subspecialty operations	198 (82.5)			
Decrease %				
0–40	45 (22.7)			
41–80	41 (20.7)			
81–100	122 (56.6)			
Decreased involvement in outpatient procedure(s) such as intravitreal therapy, laser, incision and curettage	190 (79.2)			
Decrease %				
0–40	55 (28.9)			
41–80	59 (31.3)			
81–100	76 (40.0)			

A reduction of 0–40% in trainees' involvement was classified as slight, 41–80% as severe and 81–100% as complete suppression. Chi-square test was done for the analyses.

Trainees are expected to have completed a minimum number of phacoemulsification cataract procedures by the end of training, have broad clinical exposure and be clinically competent.[11] With the reduction in surgical numbers, those who are completing ophthalmology residency or in their fellowship are the ones most affected.[12] Some may have to compensate for the deficiency by extending their training. Residency requirements are being looked into to allow YOs to progress reasonably through their programme. Any changes proposed could be shared across residency programmes to benefit YOs across the Asia-Pacific region.

The multiple enforced restrictions have created a perfect opportunity to brainstorm and reinvent the way ophthalmology is taught. New technologies can be shared among institutions. Currently, programme directors are seeking ways to re-introduce teachings on virtual platforms, and conferences are still proceeding via online formats. Courses could be provided to tutors, illustrating methods for effective online teaching. With a lack of hands-on experience during the pandemic, surgeries that do take place could be streamed for real-time learning. Surgical simulators, where available, are valuable adjuncts to hands-on training. YOs should be given protected time to attend these sessions. Virtual fellowships could be introduced, especially for fellowships affected by the pandemic. These strategies could overcome geographical boundaries and benefit a greater number of trainees.

We recognise that a limitation of this study was the number of YOs surveyed, as the percentage of YOs surveyed was not uniform across the various geographies. However, it was impractical to do so, especially in a large country like India that has more than 2,000 YOs.

In conclusion, the COVID-19 pandemic has decreased patient load, reduced exposure to surgical training, and pushed educational activities to a digital format. There is significant impact on ophthalmic training that has not been adequately addressed. Key stakeholders including academic institutions, professional bodies and YOs need to collaborate and reinvent ophthalmic education.

REFERENCES

1. Bakshi SK, Ho AC, Chodosh J, et al. Training in the year of the eye: the impact of the COVID-19 pandemic on ophthalmic education. Br J Ophthalmol 2020;104:1181-3.
2. The Royal Australian and New Zealand College of Ophthalmologists. 2020 RANZCO Examinations Timetable, 2020. Available at: https://ranzco.edu/wp-content/uploads/2020/05/Revised-2020-RANZCO-Examinations-Timetable-06052020.pdf. Accessed on 3 March 2021.
3. North West School of Surgery COVID-19 Training Disruption Notification Form. Available at: https://forms.office.com/Pages/ResponsePage.aspx?id=K5Gn_5ewMUGcD9DoB1Wyq2DExoUw6gZDq_TYdlawCSVUOUlFQlk1UlNZNk5XWVZYOUhHUUlEQ0Q5Ni4u. Accessed on 3 March 2021.
4. Amparore D, Claps F, Cacciamani GE, et al. Impact of the COVID-19 pandemic on urology residency training in Italy. Minerva Urol Nefrol 2020;72:505-9.
5. Channa R, Zafar SN, Canner JK, et al. Epidemiology of eye-related emergency department visits. JAMA Ophthalmol 2016;134:312-9.
6. Lai TH, Tang EW, Chau SK, et al. Stepping up infection control measures in ophthalmology during the novel coronavirus outbreak: an experience from Hong Kong. Graefes Arch Clin Exp Ophthalmol 2020;258:1049-55.
7. Ryder EC, Benson S. Conjunctivitis. Treasure Island, US: StatPearls Publishing; 2021.
8. Rana R, Kumawat D, Sahay P, et al. Perception among ophthalmologists about webinars as a method of continued medical education during COVID-19 pandemic. Indian J ophthalmol 2021;69:951-7.
9. Wong TY, Bandello F. Academic Ophthalmology during and after the COVID-19 Pandemic. Ophthalmology 2020;127:e51-2.
10. Hussain R, Singh B, Shah N, et al. Impact of COVID-19 on ophthalmic specialist training in the United Kingdom—the trainees' perspective. Eye (Lond) 2020;34:2356.
11. The Royal College of Ophthalmologists. Guide for delivery of Ophthalmic Specialist Training (OST), June 2018. Available at: https://www.rcophth.ac.uk/wp-content/uploads/2018/09/RCOphth-Guide-for-delivery-of-OST-version-3.5-June-2018.pdf. Accessed on 3 March 2021.
12. Potts JR. Residency and fellowship program accreditation: effects of the novel coronavirus (COVID-19) pandemic. J Am Coll Surg 2020;230:1094-7.

Wei Wei Dayna Yong [1]*MBBS*,
Teck Chang Victor Koh [1,2]*MMed (Ophth)*,
Liang Shen [3]*PhD*, Diva Kant Misra [4]*DNB*,
Wing Yun Joy Leung [5]*FCOphthHK*,
Sudhashini Chandrasekaran [6]*M Ophthal (UM)*,
Hung-Da Chou [7]*MD*, Han Nian Marcus Ang [8,9]*PhD*,
Chee Wai Wong [8,9]*PhD*

[1] Department of Ophthalmology, National University Health System, Singapore
[2] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3] Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4] EyeQ Eye Hospital, Lucknow, India
[5] Department of Ophthalmology, Tung Wah Eastern Hospital, Hong Kong
[6] Department of Ophthalmology, Faculty of Medicine, University of Malaya, Malaysia
[7] Department of Ophthalmology, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan
[8] Singapore National Eye Centre, Singapore
[9] Ophthalmology and Visual Sciences Department, Duke-NUS Medical School, Singapore

Correspondence: Dr Chee Wai Wong, Singapore National Eye Centre, 11 Third Hospital Ave, Singapore 168751.
Email: wong.chee.wai@singhealth.com.sg

Ann Acad Med Singap 2021;50:733-5
https://doi.org/10.47102/annals-acadmedsg.2021105

A rare case of thigh asymmetry in an infant

A 6-month-old baby boy presented with asymmetry of thighs since birth. On clinical examination, anteromedial aspect of the left thigh was bulky with pale yellow discolouration of the skin and no tenderness. The child was referred for high-resolution ultrasonography. On ultrasonography, there was evidence of a well-defined isoechoic soft tissue lesion measuring 1.5x6.0cm in the subcutaneous plane of the anteromedial aspect of the upper two-thirds of the left thigh with multiple cystic spaces (Fig. 1A). The lesion was noted to extend into the intermuscular fascial planes with no evidence of deeper muscle invasion (Fig. 1B). There was associated thickening of the skin and subcutaneous fat with increased echogenicity. The lesion was non-compressible on application of pressure by the ultrasonography probe. Colour Doppler ultrasonography revealed absent vascularity within the cystic spaces of the lesion (Fig. 1C).

What is your diagnosis?

A. Rhabdomyosarcoma
B. Cavernous haemangioma
C. Venous malformation
D. Arteriovenous malformation
E. Mixed lymphatic malformation

Findings and diagnosis. A diagnosis of lymphatic malformation of the thigh was made based on the findings of high-resolution ultrasonography. Lymphatic malformations tend to be infiltrative, permeate across fat planes, and manifest with associated diffuse soft tissue thickening and surrounding lymphoedema. The child was referred to the department of paediatric surgery for further management where an open surgical excision under general anaesthesia was performed. Surgical debulking of the soft tissue lesion was performed, which demonstrated intermuscular extension via the fascial planes on the subcutaneous plane of the lesion. However, there was no deeper intramuscular invasion. The intraoperative findings correlated very well with the preoperative findings on ultrasonography. Intraoperatively, the mass lesion consisted of a plethora of lymphatic vessels, some >1cm in diameter and some <1cm in diameter. Histopathology of the resected specimen demonstrated multiple macrocystic and microcystic

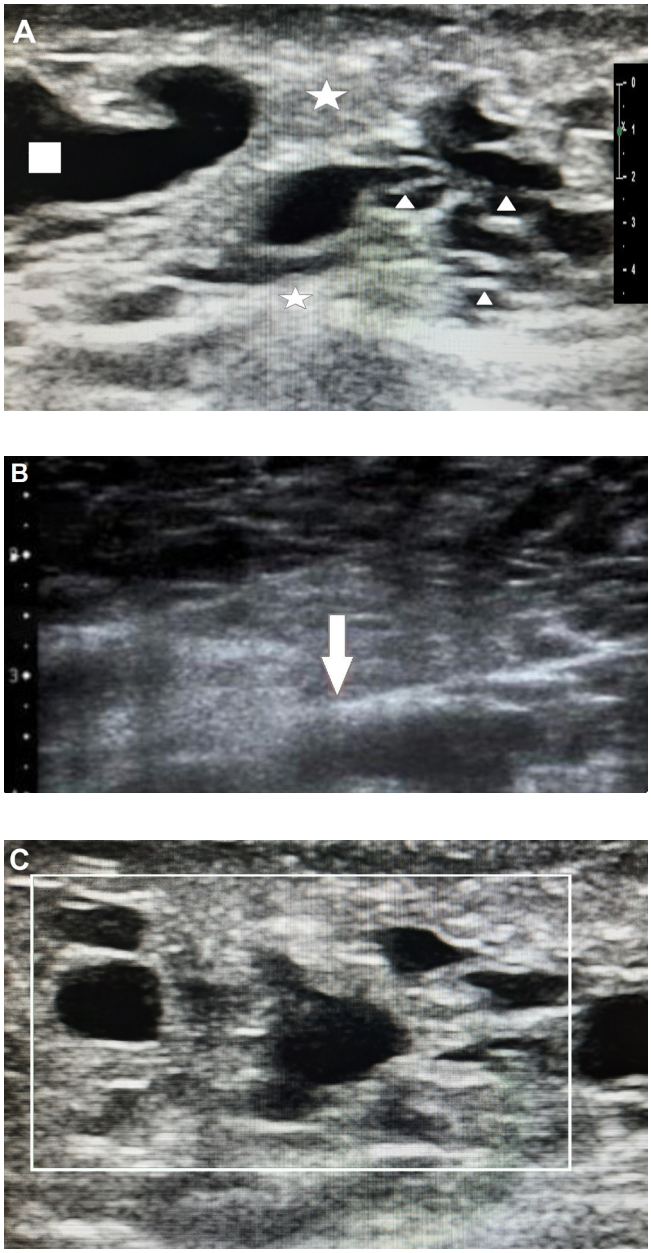


Fig. 1. (A) High-resolution ultrasonography image demonstrating an isoechoic soft tissue lesion with multiple macrocystic (e.g. area indicated by a square) and microcystic (3 arrowheads) spaces in the anteromedial aspect of the left thigh. Note the interspersed soft tissue component (2 stars). (B) Far field high-resolution ultrasonography image demonstrating the extent of the soft tissue lesion in the subcutaneous plane with extension into intermuscular fat planes (arrow). (C) Doppler ultrasonography image demonstrating absent vascularity within the cystic spaces (in rectangle box) consistent with features of lymphatic malformation.

Answer: E

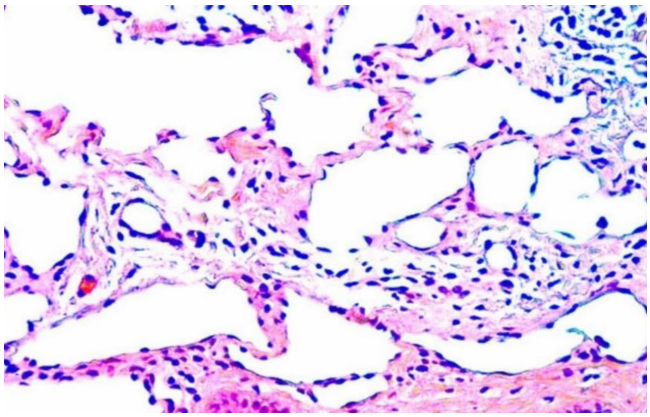


Fig. 2. Histopathology image demonstrating multiple macrocystic and microcystic lymphatic channels in the background of loose connective tissue stroma consistent with features of mixed lymphatic malformation. Note the focal disorganisation of smooth muscle in the walls of larger channels (haematoxylin and eosin staining, x200 magnification).
(Colour figure available online.)

lymphatic channels in the background of loose connective tissue stroma, consistent with features of mixed lymphatic malformation (Fig. 2). Postoperative course was uneventful and the child was discharged home after 1 week.

Discussion. Lymphatic malformations are developmental anomalies of the lymphatic system. They are benign soft tissue lesions and congenital in origin. They are also often slow growing and frequently located in proximal extremities—in this case, the trunk and axilla.[1] Lymphatic malformations are classified as macrocystic, microcystic or mixed, based on their imaging appearances.[2] Lymphatic malformation involving soft tissues can be confidently diagnosed based on high-resolution ultrasonography and colour Doppler findings, which include isoechoic to hypoechoic soft tissue masses showing multiple cystic spaces and absent vascularity. Differential diagnosis of soft tissue masses involving the extremities in the infantile age group are vascular malformations such as haemangioma (the most common); benign tumours such as lipoma; malignant tumours of the smooth muscle such as rhabdomyosarcoma; and lymphatic malformation. Lymphatic malformations do not show spontaneous resolution after birth, and first-line treatment includes sclerotherapy, with debulking surgery reserved only as second-line treatment.[3]

Although cystic lymphangiomas of congenital origin involving extremities have been previously described,[4] this case report deserves special attention due to the lymphangiomas' mixed appearance on ultrasonography. The formations were composed of large cysts interconnected with clustered smaller lymphatic cysts, which were large sized at presentation across the upper two-thirds of the thigh, a rare site for an infant. Mixed lymphatic malformation of the extremity is rare, which makes this case unique. Moreover, the lesion described is confined only to the extremity, with no abdominal extension. Literature review reveals varied presentation of the entity such as juxta-articular lymphangioma of the extremity,[5] retroperitoneal and genital lymphangioma,[6] and even acquired cases of progressive lymphangioma.[7] Previously published case reports documented abdominal lymphatic malformations extending to the extremities, mostly in autopsy specimens of preterm infants after termination of pregnancy.[8] This case illustrates an uncommon yet important cause for unilateral extremity swelling of congenital origin. Although there were complaints of asymmetry of thighs since birth in this case, the child had a delayed presentation at 6 months when the mother felt an obvious mass in the left thigh. However, prompt diagnosis of the entity on ultrasonography and timely management resulted in a favourable outcome. Since fetal lymphatic malformations carry high risk of aneuploidy and coexisting fetal malformations, prenatal diagnosis of the entity on ultrasonography has a prognostic significance.

Based on the size of the lymphatic lumen, lymphatic malformations (previously termed lymphangiomas) can be classified into microcystic lesions (previously termed lymphangioma circumscriptum), macrocystic lesions (previously termed cystic hygromas or cavernous lymphangiomas), and a combined form as described in this case. The mean diameters of cystic spaces are >1cm in macrocystic lymphatic malformation and <1cm in microcystic lymphatic malformation, and a combination of these in mixed lymphatic malformation. On ultrasonography, lymphatic malformations present as soft, easily compressible masses that increase in size in dependent positions or when venous pressures increase (through crying or the Valsalva manoeuvre). Lymphatic malformations appear as multilocular cystic masses with internal septations of varying thickness.

The cystic contents in lymphatic malformations are usually anechoic, and appear hyperechoic if debris, high lipid concentration, infection or haemorrhage is noted within. In lymphatic malformations, the cystic spaces are noted in the skin and subcutaneous fat. The cystic spaces are usually round or ovoid, rather than tubular as seen with venous malformations. Lymphatic malformations are non-compressible unlike venous malformations. On colour Doppler ultrasonography, no flow is demonstrated within the cystic spaces, but

blood flow is demonstrable in the septae. Ultrasonography including colour Doppler and spectral Doppler tracings can evaluate vascularity and determine types of vessels present in congenital vascular malformations. Soft tissue venous malformations (haemangiomas) are compressible with the typical multicystic and/or partially solid heterogeneous echotexture, and can be hypoechoic, hyperechoic, or isoechoic with respect to surrounding structures.[9] Although phleboliths are classic of venous malformation and noted on plain radiographs, they are rarely detected on ultrasonography. On colour Doppler ultrasonography, monophasic waveforms with low flow are noted in venous malformation, while continuous high flow is noted in arteriovenous malformation, and no flow is noted in large hypoechoic cysts in lymphatic malformation. The presence of pulsatile triphasic flow of nearby arteries in a venous malformation should not be confused with arteriovenous malformation. Rhabdomyosarcoma is the most common soft tissue tumour of extremities in children, and presents as a heterogeneous, well-defined and irregular mass of low to medium echogenicity on ultrasonography.[10]

Lymphatic malformations are congenital lesions, which are present since birth. Although there were complaints of asymmetry of thighs since birth in this case, the child had a delayed presentation at 6 months when the mother felt an obvious mass in the left thigh. However, prompt diagnosis of the entity on ultrasonography and timely management resulted in a favourable outcome. Lymphatic malformation needs to be included in the differential diagnosis of soft tissue masses involving the extremities, especially when the lesion is congenital and present since birth.

REFERENCES

1. Lal A, Gupta P, Singhal M, et al. Abdominal lymphatic malformation: Spectrum of imaging findings. Indian J Radiol Imaging 2016; 26:423-8.
2. Wassef M, Blei F, Adams D, et al. Vascular Anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. Pediatrics 2015;136:e203-14.
3. Okazaki T, Iwatani S, Yanai T, et al. Treatment of lymphatic malformation in children: our experience of 128 cases. J Pediatr Surg 2007;42:386-9.
4. Thakur SK. Unilocular cystic lymphangioma of thigh-an extremely rare clinical entity. Indian J Surg 2010;72:417-8.
5. Jain D, Selhi HS, Yamin M. Lymphangioma presenting as juxta-articular swelling in children: a case series. APSP J Case Rep 2013;4:30.
6. Olabanji J, Oladele A, Famurewa O, et al. Retroperitoneal and genital lymphangioma therapeutic challenges in a developing country. Libyan J Med 2009;4:44-5.
7. Larkin SC, Wentworth AB, Lehman JS, et al. A case of extensive acquired progressive lymphangioma. Pediatr Dermatol 2018;35:486-9.
8. Durukan H, Gözükara İ, Cevikoglu M, et al. Isolated fetal lymphatic malformation of the thigh: prenatal diagnosis and follow-up. Autops Case Rep 2017;7:49-53.
9. Chan YC, Giam YC. Guidelines of care for cutaneous haemangiomas. Ann Acad Med Singap 2005;34:117-23.
10. Aung LL, Soe TA, Chang KT, et al. Singapore Rhabdomyosarcoma (RMS) Experience: Shall We Change Our Practice? Ann Acad Med Singap 2014;43:86-95.

Reddy Ravikanth [1]*MD*

[1] Department of Radiology, St. John's Hospital, Kerala, India

Correspondence: Dr Reddy Ravikanth, Department of Radiology, St. John's Hospital, Kattappana South, Idukki District, Kerala 685515, India.
Email: ravikanthreddy06@gmail.com

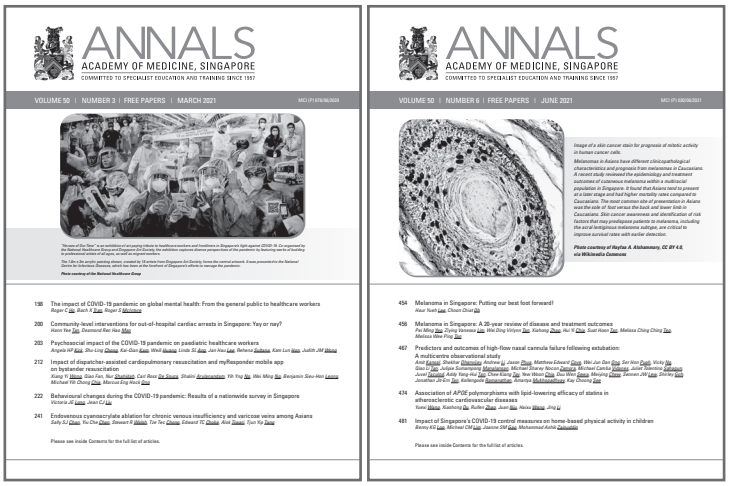
Acknowledgement

The Editorial Board of the *Annals*, Academy of Medicine, Singapore gratefully acknowledges the generous support of

The Lee Foundation

Call for Images

The *Annals* invites you to submit high-resolution images of current and historical importance in medicine, with a short caption of about 100 words. Due acknowledgement will be given to published images. Please send your photos to: annals@ams.edu.sg.



Copyright

Disclaimer

ANNALS, ACADEMY OF MEDICINE, SINGAPORE
81 Kim Keat Road, #11-00 & 12-00, NKF Centre, Singapore 328836
Tel: +65 6593 7800 | Fax: +65 6593 7867 | Email: annals@ams.edu.sg | Homepage: https://www.annals.edu.sg
Online submission: https://aams.manuscriptmanager.net/

ANNALS, ACADEMY OF MEDICINE, SINGAPORE
81 Kim Keat Road, #11-00 & #12-00 NKF Centre, Singapore 328836
Tel: +65 6593 7800 | Fax: +65 6593 7867 | Email: annals@ams.edu.sg | Homepage: https://www.annals.edu.sg