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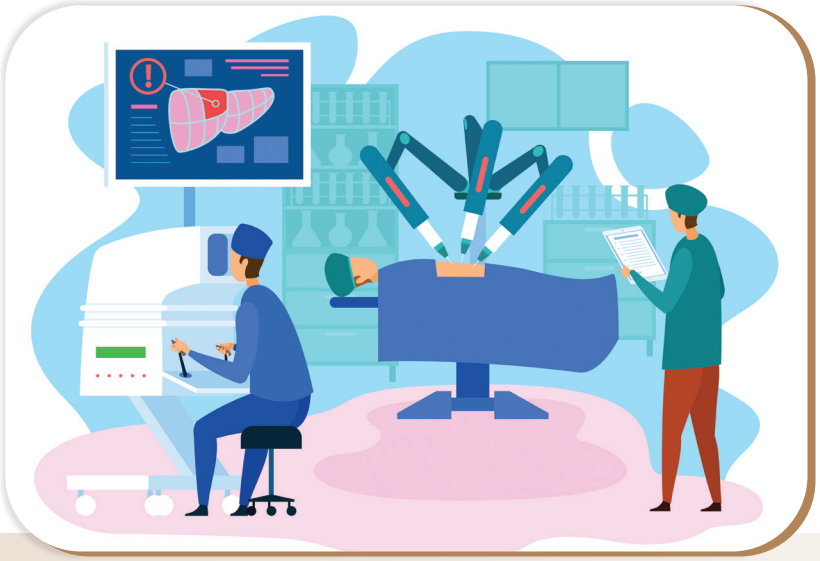

A Singapore retrospective review examined over 300 cases of laparoscopic liver resection (LLR) performed by a single surgeon without prior LLR experience. The findings revealed that open conversion rates significantly decreased among patients who underwent a totally minimally invasive approach, including robotic-assisted procedures. The study also determined trends, predictors and impact of open conversion to preempt perioperative outcomes and morbidity.

Major concerns of LLR are discussed, with learning points highlighted throughout the learning curve. In adopting such a procedure, surgeons should select cases with complexities appropriate to their level of experience to minimise the need for open conversions.

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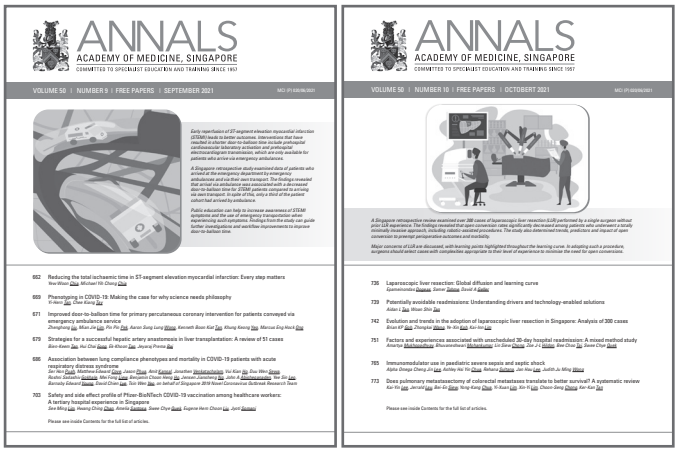

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Laparoscopic liver resection: Global diffusion and learning curve

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Laparoscopic liver resection (LLR) is being utilised with increasing frequency worldwide, as initial concerns about the safety and feasibility of LLR, such as the risk of uncontrolled major haemorrhage and potential compromise of oncologic outcomes, were not supported by the data. On the contrary, LLR was found to be associated with several significant perioperative benefits compared to open liver resection, including less blood loss, less narcotic requirement, fewer complications, and reduced hospital stay.[1,2] Knowledge of precision liver anatomy remains paramount to performing anatomically correct LLR both for hepatocellular carcinoma and colorectal cancer liver metastasis. This will achieve adequate oncologic outcomes, as outlined in the recent international consensus conference on precision anatomy for minimally invasive hepatopancreatobiliary surgery in Tokyo, Japan.[3-6] The increased utilisation of LLR is reflected in 2 worldwide literature reviews published only 7 years apart; the earlier one by Nguyen et al. in 2009 captured 2,804 patients, while a subsequent study in 2016 by Ciria et al. contained over triple the number of patients (n=9,527).[1,2] Robotic liver resection (RLR) has also emerged as a safe alternative to open liver resection with short-term clinical benefits. However, when comparing LLR to RLR, perioperative and long-term outcomes appear to be equivalent, while the cost of RLR is higher compared to laparoscopy.[7,8]

The global dissemination of LLR was highlighted by Hibi et al. in 2014 in a survey that revealed LLR was routinely performed in more than 40 countries across Asia, Europe and the Americas.[9] Their survey also revealed that the indications of LLR were expanding, as half of the participating centres were routinely performing LLR for either major hepatectomy or for resection of "difficult" posterosuperior liver segments.[10] The global diffusion of difficult LLR has continued to expand following the 2nd International Consensus Conference on Laparoscopic Liver Resection, with Ibuki et al. reporting on 4,478 difficult LLR patients from 58 centres in 19 countries between 2014 and 2018.[11] Notably, as minimally invasive donor hepatectomy is proliferating, a set of expert consensus guidelines was established to guide its safe implementation.[12] Today, worldwide interest for LLR remains strong as evidenced by the attendance of the recent International Laparoscopic Liver Society (ILLS) 2021 3rd World Congress live virtual meeting that convened in June 2021. The meeting had 1,357 registrants from 86 countries (Fig. 1). The number of registrants per continent is shown, with Asia having the most at 422 registrants, followed by Europe with 329, North America with 291, and South America with 272. The top 12 countries are listed with the US, Brazil, Mexico and Japan having the most registrants. One of the challenges in diffusing technology-dependent procedures such as LLR is the ability to implement them in low-resource countries due to lack of equipment availability and cost. Noteworthy is the participation of liver surgeons at the ILLS 2021 meeting from many low-resource countries including Bangladesh, Burundi, Costa Rica, Croatia, Estonia, Guatemala, Iran, Jamaica, Jordan, Lebanon, Lithuania, Maldives, Nigeria, Qatar, Saudi Arabia, Slovenia, Tunisia and Yemen. This is highly indicative of global diffusion of laparoscopic liver surgery interest (and hopefully utilisation) around the world.

The growth in number and complexity of LLR and its adoption by surgeons without prior experience in minimally invasive liver surgery prompted efforts to delineate the learning curve of LLR, defined as improvement in performance over time. Performance metrics that have been used in the LLR learning curve literature included operating room (OR) time, intraoperative estimated blood loss, conversion to open hepatectomy and postoperative morbidity. However, not all studies report on all the above parameters and therefore one must exercise caution when comparing between different learning curve series. Furthermore, the learning curve will vary based on case difficulty and the surgeon's prior experience with open hepatobiliary surgery and minimally invasive surgery.[13,14] Vigano et al. looked into the need for conversion to an open approach and discovered that the learning curve of laparoscopic minor hepatectomy for a self-taught surgeon is 60 cases.[15] Regarding laparoscopic major hepatectomy, Nomi et al. focused

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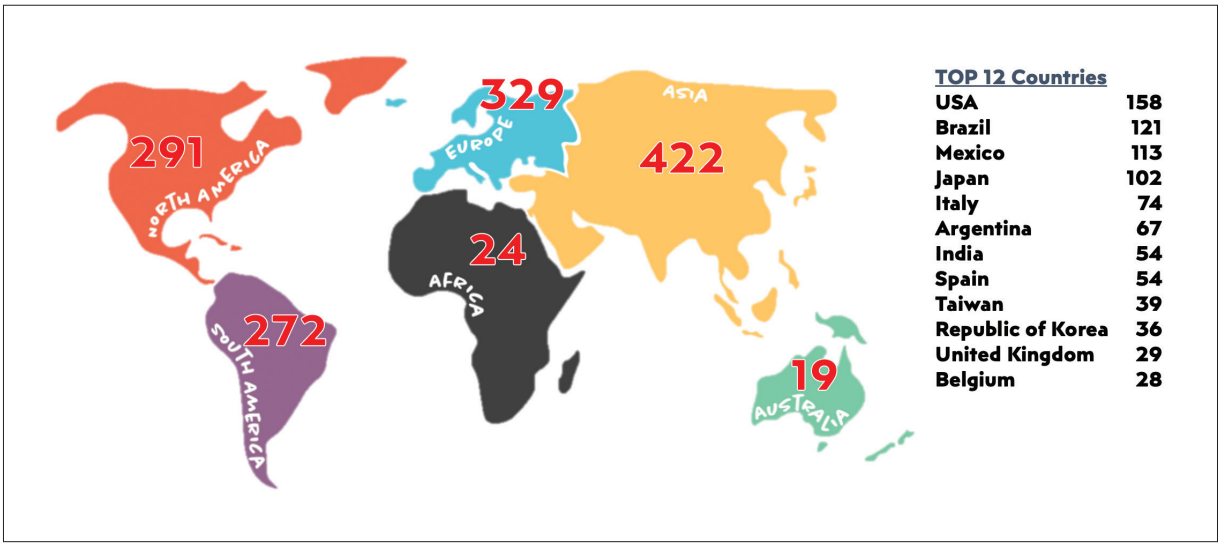

Fig. 1. Global map of registrants for the International Laparoscopic Liver Society 2021 3rd World Congress live virtual meeting that convened in June 2021. The meeting had 1,357 registrants from 86 countries. The top 12 countries are listed.

on OR time as a metric in 173 laparoscopic major hepatectomies and found that their learning curve spanned 45–75 cases.[16] Their findings were corroborated by van der Poel et al. who looked into their own 159 laparoscopic major hepatectomies, and using the need for conversion as a metric, defined their learning curve as 55 cases.[17]

In one of the largest LLR series published to date, Swaid et al. reported on the University of Pittsburgh Medical Center experience with 1,062 LLR patients spanning almost 2 decades (2001–2017).[18] The authors examined performance over time and divided the study cohort into 3 periods: 2001–2007 (n=203), 2008–2012 (n=426) and 2013–2017 (n=433). They found that over the study period, a greater percentage of overall hepatectomies were performed laparoscopically despite operating on more patients with background liver cirrhosis. Furthermore, a greater percentage of LLR were accomplished in a pure laparoscopic fashion, while OR time, need for transfusion and postoperative complications decreased. Analysing the literature, cumulative sum analysis factoring OR time and the need for conversion revealed that the learning curve exhibited 2 phases; 45 cases were required to break through the initial learning curve, but a total of 60–70 cases were required to further progress into the standardisation "mastery" phase that includes major hepatectomy and difficult segments. Therefore, the authors recommend that surgeons, who are still in their initial learning curve, start with laparoscopic minor hepatectomy, including left lateral sectionectomy, and after 45 cases they can progress to laparoscopic major hepatectomy or partial hepatectomy of the difficult posterosuperior segments. More complex resections, such as laparoscopic live-donor hemi-hepatectomy, should be undertaken only when the "mastery" phase is reached.

In this issue of the *Annals*, Goh et al. report on a sizable single surgeon series of 310 consecutive patients who underwent LLR from 2011 to 2021.[19] Of note, although the surgeon had no prior experience in LLR, he was experienced in open hepatobiliary surgery and complex minimally invasive abdominal surgery. The study data encompass all relevant clinicopathologic factors, including the Iwate and Institut Mutualiste Montsouris (IMM) difficulty score grading of the resections, and all pertinent perioperative metrics are reported, such as OR time, blood loss, need for transfusion, conversion to open approach and morbidity. The authors report excellent outcomes, with a low rate of margin positive resection (3.1%) and only 2 in-hospital mortalities in the entire cohort. As the existing literature points to about a 60-case requirement to navigate the LLR learning curve, the authors further subdivided their cohort in 5 chronologically consecutive groups of 60 patients each. They discovered that over time, LLR was performed on higher risk patients (older age, higher American Society of Anesthesiologists score, and increased frequency of portal hypertension) requiring technically more demanding resections (larger tumour size). Despite this, they noted improved outcomes over the study

period: decrease in the open conversion rate, blood loss and blood transfusion rate. The importance of the initial LLR learning curve was again demonstrated in the analysis of factors associated with conversion to an open approach, where only surgeon experience with <60 cases and IMM difficulty score of III were independent predictors of open conversion on multivariate analysis.

In summary, LLR is being increasingly utilised across the world. The initial learning curve for surgeons without previous experience in LLR is steep and requires 45–70 cases. Increased surgeon experience is associated with improvement in perioperative outcomes despite operating on higher-risk patients and performing more complex resections. It is likely that the learning curve of the "second generation" aparoscopic liver surgeons who are trained by surgeons already experienced in LLR will be shorter, but that remains to be studied.

REFERENCES

1. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection - 2,804 patients. Ann Surg 2009;250:831-41.
2. Ciria R, Cherqui D, Geller DA, et al. Comparative Short-term Benefits of Laparoscopic Liver Resection. Ann Surg 2016;263:761-77.
3. Ciria R, Berardi G, Nishino H, et al. A snapshot of the 2020 conception of anatomic liver resections and their applicability on minimally invasive liver surgery. A preparatory survey for the Expert Consensus Meeting on Precision Anatomy for Minimally Invasive HBP Surgery. J Hepatobiliary Pancreat Sci 2021. doi:10.1002/jhbp.959.
4. Morimoto M, Tomassini F, Berardi G, et al. Glissonean approach for hepatic inflow control in minimally invasive anatomic liver resection: A systematic review. J Hepatobiliary Pancreat Sci 2021. doi:10.1002/jhbp.908.
5. Monden K, Alconchel F, Berardi G, et al. Landmarks and techniques to perform minimally invasive liver surgery: A systematic review with a focus on hepatic outflow. J Hepatobiliary Pancreat Sci 2021. doi:10.1002/jhbp.898
6. Wakabayashi T, Cacciaguerra AB, Ciria R, et al. Landmarks to identify segmental borders of the liver: A review prepared for PAM-HBP expert consensus meeting 2021. J Hepatobiliary Pancreat Sci 2021. doi:10.1002/jhbp.899.
7. Ziogas IA, Evangeliou AP, Mylonas KS, et al. Economic analysis of open versus laparoscopic versus robotic hepatectomy: a systematic review and meta-analysis. European J Heal Econ 2021;22:585-604.
8. Ziogas IA, Giannis D, Esagian SM, et al. Laparoscopic versus robotic major hepatectomy: a systematic review and meta-analysis. Surg Endosc 2021;35:524-35.
9. Hibi T, Cherqui D, Geller DA, et al. International Survey on Technical Aspects of Laparoscopic Liver resection: a web-based study on the global diffusion of laparoscopic liver surgery prior to the 2nd International Consensus Conference on Laparoscopic Liver Resection in Iwate, Japan. J Hepatobiliary Pancreat Sci 2014;21:737-44.
10. Hibi T, Cherqui D, Geller DA, et al. Expanding indications and regional diversity in laparoscopic liver resection unveiled by the International Survey on Technical Aspects of Laparoscopic Liver Resection (INSTALL) study. Surg Endosc 2016;30:2975-83.
11. Ibuki S, Hibi T, Tanabe M, et al. Short-term Outcomes of "Difficult" Laparoscopic Liver Resection at Specialized Centers: Report From INSTALL (International Survey on Technical Aspects of Laparoscopic Liver Resection)-2 on 4478 Patients. Ann Surg 2020. doi:10.1097/SLA.0000000000004434.
12. Cherqui D, Ciria R, Kwon CHD, et al. Expert Consensus Guidelines on Minimally Invasive Donor Hepatectomy for Living Donor Liver Transplantation From Innovation to Implementation: A Joint Initiative From the International Laparoscopic Liver Society (ILLS) and the Asian-Pacific Hepato-Pancreato-Biliary Association (A-PHPBA). Ann Surg 2021;273:96-108.
13. Cheek SM, Geller DA. The Learning Curve in Laparoscopic Major Hepatectomy: What Is the Magic Number? JAMA Surg 2016;151:929.
14. Brown KM, Geller DA. What is the Learning Curve for Laparoscopic Major Hepatectomy? J Gastrointest Surg 2016; 20:1065-71.
15. Vigano L, Laurent A, Tayar C, et al. The Learning Curve in Laparoscopic Liver Resection. Ann Surg 2009;250:772-82.
16. Nomi T, Fuks D, Kawaguchi Y, et al. Learning curve for laparoscopic major hepatectomy. Brit J Surg 2015;102:796-804.
17. MJ van der Poel, Besselink MG, Cipriani F, et al. Outcome and Learning Curve in 159 Consecutive Patients Undergoing Total Laparoscopic Hemihepatectomy. JAMA Surg 2016;151:923.
18. Swaid F, Sucandy I, Tohme S, et al. Changes in Performance of More Than 1000 Minimally Invasive Liver Resections. JAMA Surg 2020;155:986-8.
19. Goh BKP, Wang Z, Koh YX, et al. Evolution and trends in the adoption of laparoscopic liver resection in Singapore: Analysis of 300 cases. Ann Acad Med Singap 2021;50:742-50.

EDITORIAL

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Potentially avoidable readmissions: Understanding drivers and technology-enabled solutions

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Hospital admissions place high resource demands on the health system, and is a major cost-driver in Singapore and globally.[1-3] Admissions have and will continue to increase given Singapore's ageing population and growing chronic disease and multimorbidity burden, impacting care quality and patient/provider experience.[2,4] While majority of admissions are clinically appropriate and unavoidable as part of care provision,[1,2,4] a significant proportion are readmissions for conditions arising from potentially avoidable issues occurring during the initial admission, discharge or post-admission.[1,3,5] Recognising this, Singapore included 30-day readmission rates in its performance measure and quality improvement framework for acute hospitals in 2011.[1] However, healthcare expenditure continued to increase, doubling from SGD4 billion in 2011 to SGD10 billion in 2018, and was projected to triple by 2020 (SGD12 billion).[2] Hence, research into effective reduction in high-cost drivers (30-day readmissions) remains imperative to ensure long-term sustainability.

The concept of potentially avoidable readmissions (PARs) is readily understood and widely applied.[1,3] However, identification is difficult, requiring determination of clinical appropriateness within a given system structure and resources, subject to the greater environment and culture it is nested in.[3,6] Combined with the massive volume of admissions annually, manual identification is impossible.

Administrative database algorithms from international or Singapore literature allow automation of this process.[3,6] These algorithms allow a more objective identification of PARs and their prevalence, assuming such a readmission could be identified with certainty. Two approaches exist: including cases as avoidable if they match predefined a priori criteria, e.g. readmissions with the same diagnosis, and excluding admissions predefined as unavoidable, e.g. trauma, neonatal or obstetric care.[3,6] The former is highly specific and identifies a much smaller number of cases but with definite preventability, while the latter is highly sensitive and identifies a large number of cases but with varying preventability. Given that preventability greatly depends upon context, the latter approach is suitable for primary screening, with further refinement of results based on local factors. One such algorithm is SQLape, upon which various internationally validated predictive scoring systems (LACE, HOSPITAL) were derived, allowing identification of patients for intervention before they incur high costs.[3,6]

However, such scores have demonstrated varying predictive accuracy, likely due to the overly simplified model variables. Out of practical necessity, many predictive scores are derived from administrative databases of routinely collected clinical and socio-demographic data; such data are often not comprehensive enough to adequately capture the full complexity of drivers leading to PARs.[2,6] Omission of social and environmental factors may impact identification accuracy and predictive ability.[6] Additionally, such factors are often specific to the Singapore context, reflecting the social, cultural and legal structures, which necessitate in-depth contextual research to uncover.[2]

PARs reflect a confluence of contextual issues at multiple levels: patient/individual, care provider, health system structure, and larger sociocultural environment.[2] Both qualitative and quantitative methodologies are therefore essential to identify and measure the impact of these factors.

The findings by Mukhopadhyay et al. in this issue of the *Annals* reflect the growing recognition of socio-psychoeconomic influences upon health and clinical outcomes.[7] In their mixed method study, aside from quantitative characteristics available from routine data, they attempted to uncover the qualitative differences in care journey experiences between patients with and without readmissions within 30 days. Patients with readmissions expressed more negative psychological reactions and perceptions: a more fatalistic outlook; neglect and uninvolved in care decisions; low trust in treatments; and lesser health literacy.

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These echo the growing body of literature, where patient psychology and perceptions and their community/home environments influence observed health outcomes.[2] These findings help build a body of evidence towards a more complete understanding of PAR drivers, and thereby increase our confidence in identification and prediction of such PARs.

Evidence suggests that reduction of PARs is possible through improvements in care quality, discharge processes and care transitions between providers in a patient-centric manner. However, it is hubris to state that all such PARs are preventable. Just as PARs are driven by a complexity of factors, interventions to prevent them would be similarly or even more so. Not all drivers are modifiable at a cost proportionate to the readmission avoided; others may require intervention at a systems or whole-society level.[2,8,9]

In Singapore, interventions aimed at preventing PARs are currently focused on improving care transitions via integration between providers, thereby allowing smoother discharges between care sectors and reducing the number of patients who fail to transit between providers. One such intervention is the Hospital-to-Home (H2H) programme launched in April 2017.[9]

The H2H programme supports care transition between hospital and health service providers through the aid of a "patient-navigator" nurse and multidisciplinary care team. Patients are identified as high-risk based on algorithm scores during their initial hospital admission. These high-risk patients are then evaluated by the H2H team prior to discharge. Based on the various care needs identified and the caregivers' capability, a comprehensive care plan is made, drawing upon community care resources such as home nursing or social services as necessary.

With a reported 8,000 patients supported within a year of its roll-out, the H2H programme has seen mixed effects with some patient groups showing little or even negative outcomes.[8,9] Such programmes are primarily targeted towards a patient's medical/nursing needs and smoothening transitions between clinical providers, but often fails to address other modifiable drivers arising at the patient-level (perceptions, psychology), socioeconomic environment (income, housing), physical environment (built resources, mobility access) and the greater society (discrimination, social norms, legal and ethical structures).[8,9]

These results indicate the necessity of understanding the wide span of needs across different patient groups, which may extend beyond just the clinical condition.[2,8,9] Transforming the patient's role from a passive recipient into an active participant in their care may further aid this process.[10]

Another issue lies in how technology is used (or not used) as an enabler. Current scoring systems are geared solely towards identification of patients-at-risk, as in the H2H programme. This is an important first step, but doing so merely identifies the individual and fails to pinpoint the underlying reasons or domains driving this risk.[2,3,6] Prediction alone is insufficient. This early truncation of digitalisation as an enabler may partially explain the lackluster results observed. The H2H programme relies on assessors and human judgement to determine care needs. Without addressing the underlying drivers, intervention efforts would be misdirected and fail to evidence effectiveness. This therefore places a huge burden on the assessing team to be as comprehensive as possible, a particularly difficult task given the wide-spanning complexity of patient needs and perceptions across more than just the clinical conditions.

These programmes are also highly resource intensive, given the high provider-to-recipient ratio and number of services such recipients require for their complex care needs.[8] It is therefore necessary to ensure that intervention efforts are appropriately directed, maximising savings from PARs avoided while minimising intervention costs. Thus, beyond leveraging technology as a prediction tool, it should be used as an enabler for interventions. Accurate and up-to-date near real-time scoring metrics should be paired with evidence-based bundled interventions across the entire patient journey.[5,6]

An example of how technology as an enabler could be fully utilised was implemented in a regional acute hospital.[5] Using a Singapore-derived readmission risk score, the score and its risk components were embedded within the hospital's electronic medical records on a real-time basis. This allowed flagging of high-risk patients to care providers, identification of modifiable components driving the risk, and initiation of evidence-based bundled interventions specific for each risk-strata; thereby most effectively and efficiently reducing readmission risk.[5]

In recent years, the benefits of electronic medical records and big data are increasingly evident as supports towards an intelligent and integrated care system. They can be a powerful tool towards reducing PARs if appropriately applied in a problem-focused manner across the entire patient care journey. In the above hospital, the technology was employed as an enabler towards improving patient care: at the start of admission (risk prediction), during the admission (areas for intervention) and discharge (reduction in risk).[5] Future work should include the patients' and caregivers' perspectives, either from clinical team inputs or via artificial intelligence algorithms in big data, to

encompass risk drivers for improved prediction and solution generation.

Reducing PARs is a potential area for decreasing health system demand and cost. However, current scoring methods for identification and prediction of PAR risk is limited. Recent research shows the great complexity and interplay between socio-psychoeconomic influences driving this risk, elicitable from patient/caregiver perspectives. Engaging patients and caregivers as active partners in care is essential. Beyond simply flagging patients as high-risk based on prediction, digitalisation can and should be utilised as an enabler for interventions, informed by and targeted towards these drivers across the care journey.

REFERENCES

1. Lim E, Matthew N, Mok W, et al. Using hospital readmission rates to track the quality of care in public hospitals in Singapore. BMC Health Serv Res 2011;11(Suppl 1):A16.
2. Low LL, Tay WY, Ng MJM, et al. Frequent hospital admissions in Singapore: Clinical risk factors and impact of socioeconomic status. Singapore Med J 2018;59:39-43.
3. Yam CH, Wong EL, Chan FW, et al. Measuring and preventing potentially avoidable hospital readmissions: A review of the literature. Hong Kong Med J 2010;16:383-9.
4. Low LL, Liu N, Lee KH, et al. FAM-FACE-SG: A score for risk stratification of frequent hospital admitters. BMC Med Inform Decis Mak 2017;17:35.
5. Wu CX, Suresh E, Phng FWL, et al. Effect of a real-time risk score on 30-day readmission reduction in Singapore. Appl Clin Inform 2021;12:372-82.
6. Zhou H, Della PR, Roberts P, et al. Utility of models to predict 28-day or 30-day unplanned hospital readmissions: An updated systematic review. BMJ Open 2016;6:e011060.
7. Mukhopadhyay A, Mohankumar B, Chong LS, et al. Factors and experiences associated with unscheduled 30-day hospital readmission: A mixed method study. Ann Acad Med Singap 2021:50:751-64.
8. Ang YH, Ginting ML, Wong CH, et al. From hospital to home: Impact of transitional care on cost, hospitalisation and mortality. Ann Acad Med Singap 2019;48:333-7.
9. Ng SCW, Kwan YH, Yan S, et al. The heterogeneous health state profiles of high-risk healthcare utilizers and their longitudinal hospital readmission and mortality patterns. BMC Health Serv Res 2019;19:931.
10. Senot C, Chandrasekaran A, Ward P, et al. The impact of combining conformance and experiential quality on hospitals' readmissions and cost performance. Management Science 2015;62:829-48.
11. Low LL, Vasanwala FF, Ng LB, et al. Effectiveness of a transitional home care program in reducing acute hospital utilization: A quasi-experimental study. BMC Health Serv Res 2015;15:100.

ORIGINAL ARTICLE

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Evolution and trends in the adoption of laparoscopic liver resection in Singapore: Analysis of 300 cases

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ABSTRACT

Introduction: The introduction of laparoscopic surgery has changed abdominal surgery. We evaluated the evolution and changing trends associated with adoption of laparoscopic liver resection (LLR) and the experience of a surgeon without prior LLR experience.

Methods: A retrospective review of 310 patients who underwent LLR performed by a single surgeon from 2011 to 2020 was conducted. Exclusion criteria were patients who underwent laparoscopic liver surgeries such as excision biopsy, local ablation, drainage of abscesses and deroofing of liver cysts. There were 300 cases and the cohort was divided into 5 groups of 60 patients.

Results: There were 288 patients who underwent a totally minimally invasive approach, including 28 robotic-assisted procedures. Open conversion occurred for 13 (4.3%) patients; the conversion rate decreased significantly from 10% in the initial period to 3.3% subsequently. There were 83 (27.7%) major resections and 131 (43.7%) resections were performed for tumours in the difficult posterosuperior location. There were 152 (50.7%) patients with previous abdominal surgery, including 52 (17.3%) repeat liver resections for recurrent tumours, and 60 patients had other concomitant operations. According to the Iwate criteria, 135 (44.7%) were graded as high/expert difficulty. Major morbidity (>grade 3a) occurred in 12 (4.0%) patients and there was no 30-day mortality. Comparison across the 5 patient groups demonstrated a significant trend towards older patients, higher American Society of Anesthesiologists (ASA) score, increasing frequency of LLR with previous abdominal surgery, increasing frequency of portal hypertension and huge tumours, decreasing blood loss and decreasing transfusion rate across the study period. Surgeon experience (≤60 cases) and Institut Mutualiste Montsouris (IMM) high grade resections were independent predictors of open conversion. Open conversion was associated with worse perioperative outcomes such as increased blood loss, transfusion rate, morbidity and length of stay.

Conclusion: LLR can be safely adopted for resections of all difficulty grades, including major resections and for tumours located in the difficult posterosuperior segments, with a low open conversion rate.

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Keywords: Laparoscopic hepatectomy, laparoscopic liver resection, robotic hepatectomy, robotic liver resection, Singapore

INTRODUCTION

Over the past few decades, the introduction of laparoscopic surgery has been the biggest game changer in abdominal surgery.[1] However, although the first laparoscopic liver resections (LLR) were reported in the early 1990s,[2,3] widespread adoption of LLR was met with initial skepticism due to technical concerns and the fear of uncontrollable intraoperative bleeding.[4-7] Furthermore, concerns were raised regarding the use of LLR for hepatic malignancies due to the potential for compromise in resection margins and oncological outcomes.[8,9] Nonetheless, despite these initial hesitancies, the adoption of LLR has rapidly increased over the past decade[10] and LLR has become the standard approach today in many specialised liver centres, especially for minor liver resections for tumours in anterolateral

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CLINICAL IMPACT

What is New

- Surgeon experience and difficulty level of liver resections predicted the need for conversion to open surgery.
- Laparoscopic liver resection can be safely performed for liver resections of all difficulty levels including resection of tumours located in the posterosuperior liver segments.

Clinical Implications

- In carefully selected patients, laparoscopic liver resection can be safely performed with a low rate of open conversion.

segments.[11,12] Several consensus meetings convened by experts and pioneers in LLR over the past decade have provided recommendations for the development and safe dissemination of LLR.[12-14]

The first LLR was performed in Singapore only in 2004.[15] The uptake of LLR was slow for the next 7–8 years and only a small number of cases were performed annually.[15] These were mainly limited to minor resections for tumours in the anterolateral segments.[15] However, in line with global trends, there was a rapid increase in LLR in institutions in Singapore since 2012, including its use in major hepatectomies.[15,16] In 2017, the first large series of LLR documenting 195 resections was published.[17]

The primary objective of the current study was to analyse a single surgeon's experience with the adoption of LLR and its evolution. The secondary objective was to determine predictive factors and the impact of open conversion after LLR.

METHODS

This is a retrospective review of 310 consecutive patients who underwent LLR performed by a single surgeon from 2011 to 2020. The study was approved by the hospital's institution review board and all data were obtained from a prospective surgical database. The inclusion criteria included all patients who underwent LLR. This included conventional multiport LLR, robotic-assisted LLR, hand-assisted LLR and laparoscopic-assisted resections (hybrid, laparoscopic mobilisation and open parenchymal transection). Exclusion criteria were patients who underwent laparoscopic liver surgeries such as excision biopsy, local ablation, drainage of abscesses and deroofing of liver cysts. Similarly, LLR for unique circumstances such as biliary pathology requiring biliary-enteric anastomoses, vascular reconstruction or donor hepatectomies were excluded.

Prior to the study, the surgeon had no prior experience or formalised training in performing LLR. This study represents an updated experience from a previous report[18] of the surgeon's surgical training and operation technique.[18,19] All the resections in this series were performed without a proctor. Only cases where the surgeon was the senior surgeon performing most of the procedure or key parts of the procedure were included in the series. Surgeries where the surgeon acted as a tutor or assistant for colleagues were not included. As the hospital is an academic institution, many of the LLR or parts of the procedure can be performed by surgical residents or fellows under direct supervision.

Definitions

Postoperative morbidity was classified and graded according to the Clavien-Dindo system.[20] All postoperative morbidity was recorded up to 30 days or during the index hospital stay, with 30-day readmissions also recorded. The totally laparoscopic approach included any procedure that was attempted by conventional laparoscopy, while the robotic-assisted LLR included any procedure whereby the robot was docked. Open conversion was defined as any LLR whereby the preoperative plan was for laparoscopic resection but the procedure had to be completed (for mobilisation or transection) via an open incision regardless of the length of the incision.

The extent and type of liver resections were classified according to the Brisbane classification published in 2000 whereby a major hepatectomy was defined as a resection of ≥3 contiguous segments.[21] Additionally, as previously reported,[18,19,22] resections of segments 6/7 (right posterior sectionectomies) and segments 5/8 (right anterior sectionectomies) were considered as technical major hepatectomies. Segments 1/4a/7/8 were considered posterosuperior segments whereas segments 2/3/4b/5/6 were considered as anterolateral segments. The LLR were also classified according to the Iwate difficulty scoring system[23] and Institut Mutualiste Montsouris (IMM) system.[24]

Statistical analysis

LLR was divided into 5 consecutive equal groups of 60 patients. This was based on the findings of previous studies,[4,18] which reported that the learning curve of

LLR was approximately 60 cases. All statistical analyses were performed using SPSS Statistics software version 21.0 (IBM Corp, Armonk, US). The Jonckheere-Terpstra test or Mantel Haenszel test were used as appropriate. Univariate analyses were performed using chi-square tests, Fischer's Exact test or Mann-Whitney U tests. Multivariate analyses were performed on factors that were significant (P<0.05) on univariate analyses. Logistic regression analyses were used to perform multivariate analyses. All statistical tests were 2-sided and P<0.05 was considered statistically significant.

RESULTS

During the study period, 300 LLR that met the study criteria were included (Table 1). The baseline clinicopathologic features and outcomes of the patients are summarised in Table 2. Seven of 228 patients (3.1%) with malignant tumours had resection margins <1mm. There was no 30-day mortality but there were 2 in-hospital mortalities. The first mortality occurred in a patient with end-stage renal failure on dialysis and liver cirrhosis who underwent minor LLR for liver cancer. The surgery and initial postoperative recovery were uneventful. However, due to social reasons, the patient could not be discharged and unfortunately acquired nosocomial pneumonia several weeks after surgery and eventually demised from sepsis. The second mortality occurred in an elderly patient with ischaemic heart disease and chronic obstructive lung disease who underwent right posterior sectionectomy for colorectal metastases. The operation time was 300 minutes and the estimated blood loss was 300mL. Unfortunately, he developed early postoperative cerebrovascular accident with hemiparesis. He was successfully stabilised but while awaiting placement at a rehabilitation facility, he acquired viral pneumonia and demised from respiratory failure despite ventilatory support.

Evolution and changing trends across the study period

Across the study period, we observed significant changes in the baseline clinicopathological features and perioperative outcomes of the patients. Patients were significantly older, of higher American Society of Anesthesiologists (ASA) score, were more likely to have previous abdominal surgery, more likely to undergo totally minimally invasive surgical procedure, more likely to have huge (≥90mm) tumours and have an increasing incidence of portal hypertension over the study period. This was also associated with a significant decrease in median blood loss and blood transfusion rate over time.

Predictors and outcomes of open conversion

Thirteen patients experienced open conversion and this was for bleeding (n=6), tumour extent and unclear margins (n=2), slow progress (n=2), difficulty localising tumour (n=1) and dense adhesions (n=2) (Table 3). Only surgeon experience (≤60 cases) and high grade were independent predictors of open conversion on multivariate analyses. Patients who underwent open conversion had significantly increased blood loss, transfusion rate, postoperative morbidity and major morbidity, and postoperative length of stay.

DISCUSSION

We report in this study a single surgeon's experience with the adoption of LLR over the past decade. Over time, LLR was performed on significantly higher risk patients requiring technically more demanding resections (older age, higher ASA score, increased frequency of portal hypertension, increased frequency of huge tumours, and increased frequency of patients with previous abdominal surgery). Despite this, there was a significant decrease in the open conversion rate, blood loss and blood transfusion rate.

Interestingly, it is worth highlighting that the proportion of high difficulty cases did not change significantly over time. During the first 60 cases, 45% of the cases were graded according to the Iwate criteria as high or expert level, and 38% of the cases were performed for tumours located in the difficult posterosuperior segments. However, the open conversion rate was only 10%. This was possible as we had utilised the hand-assisted or laparoscopic-assisted (hybrid) technique in 9 cases (15%) during our early experience, enabling us to perform complicated resections successfully early on in our learning curve. In our opinion, the hand-assisted and hybrid approaches enabled us to embark safely on difficult LLR and were extremely useful as an initial stepping stone towards performing difficult hepatectomies fully laparoscopically.[18]

A major obstacle to the widespread dissemination of LLR is the long steep learning curve reported by pioneering surgeons. In a landmark paper from France in 2009,[4] Vigano et al. reported that the learning curve of minor LLR in terms of open conversion rate was 60 cases. Open conversion rates for minor LLR decreased from 15.5% to 10.5% after approximately 60 cases and further decreased to 3.4% after 116 cases. This long steep learning curve was similarly reported by other pioneer surgeons.[25] In Japan, Hasegawa et al. reported their institution learning experience with 245 LLR.[5] They revealed that major hepatectomies could

Table 1. Types of laparoscopic liver resection in 300 patients

Resection type	No. (%)
Minor hepatectomy (n=218)	
Wedge resection – anterolateral segments	75 (25.0)
Wedge resection – posterosuperior segments	30 (10.0)
Left lateral sectionectomy	41 (13.7)
Segmentectomy/bisegmentectomy – anterolateral segments	43 (14.3)
Segmentectomy/bisegmentectomy – posterosuperior segments	29 (9.7)
Major hepatectomy (n=82)	
Right posterior sectionectomy (segment 6/7)	27 (9.0)
Right anterior sectionectomy (segment 5/8)	8 (2.7)
Left hepatectomy ± caudate	13 (4.3)
Extended left hepatectomy ± caudate	3 (1.0)
Right hepatectomy ± caudate	23 (7.7)
Extended right hepatectomy ± caudate	1 (0.3)
Central hepatectomy	7 (2.3)

be attempted safely only after having performing 64 minor hepatectomies. This stepwise approach resulted in excellent outcomes associated with the 44 laparoscopic major hepatectomies performed subsequently with an open conversion rate of 6.8% and low major morbidity rate of 13.6%. Concordant with these findings, Nomi et al., who used cumulative sum analysis, reported that the single surgeon learning curve of a pioneering surgeon in terms of operation time was 45–75 cases for major hepatectomies, even after the surgeon had acquired sufficient experience with minor hepatectomies.[26]

More recently, a multicentre European study compared the learning curve according to length of stay between 4 pioneering surgeons in stage 2, with 4 early adopting surgeons in stage 3 of the IDEAL (idea, development, exploration, assessment and long-term follow-up) framework.[27] The study reported that the early adopting surgeon could achieve comparable outcomes after only 46 cases compared to the pioneering surgeon's 150 cases.[27] Similarly, the findings of a recent systematic review analysing the learning curves of LLR supported these findings and reported that the number of cases needed to surmount the learning curve of LLR steadily decreased over time.[28] The study also suggested that the learning curve of robotic-assisted liver resections seemed to be shorter than conventional LLR.

The findings of the present study similarly indirectly support the observations of these recent studies that the learning curve for the modern-day surgeon is much shorter than that of pioneering surgeons.[18,27,28] Despite a high proportion of patients requiring complicated resections such as resections with a high difficulty score,[29] major LLR,[30] repeat LLR,[19] cirrhosis[31] and huge tumours[32] in our early experience, the LLR could be completed successfully with a low open conversion rate and low morbidity. It is important to add that in our analysis, we have intentionally included the different approaches for minimally invasive liver resections, including hand-assistance and robotic-assistance, to reflect the real-world situation.[18] Confining the analysis to a particular approach such as conventional laparoscopy and excluding other cases performed by other minimally invasive surgical approaches may mislead the reader on the number of cases and outcomes during the learning curve.

One of the major concerns with LLR is the occurrence of unplanned open conversions. This is most commonly reported to be due to intraoperative bleeding.[33-35] During a surgeon's early learning curve, a high open conversion rate especially from bleeding could theoretically negate many of the benefits of LLR and could even result in poorer perioperative outcomes.[34,35] In our study, surgeon experience and IMM high grade procedures were the only independent predictors of open conversion. Concordant with the findings from previous published studies,[33,34] we found that the need for open conversion resulted in poorer perioperative outcomes such as increased blood loss, higher transfusion rate, longer operation time, longer postoperative stay and higher postoperative morbidity rate. These findings highlight the importance for surgeons embarking on LLR to select cases with complexities appropriate to their level of experience to minimise the need for open conversion.

In our experience, most of the open conversions for bleeding were due to slow progress and persistent slow oozing without the need for emergency conversion. It is imperative that surgeons embarking on LLR learn the techniques of controlling bleeding intracorporeally (even if temporarily) prior to open conversion. Various techniques such as compression with gauze or other mechanical haemostats, application of clips, suturing, elevation of the liver and finger compression (hand-

Table 2. Baseline and outcomes across the 5 groups of 300 consecutive patients who underwent laparoscopic liver resection

	Total N=300	**Group 1 (1–60)**	**Group 2 (61–120)**	**Group 3 (121–180)**	**Group 4 (181–240)**	**Group 5 (240–300)**	***P* value**
Age, median (IQR), years	64 (14)	61 (18)	65 (13)	64 (10)	67 (15)	64 (17)	**0.008**
Male sex, no. (%)	195 (65.0)	23 (38.3)	19 (31.7)	22 (36.7)	20 (33.3)	21 (25.0)	0.798
Totally MIS (laparoscopic and robotic), no. (%)	289 (96.3)	51 (85.0)	60 (100)	60 (100)	58 (96.7)	60 (100)	**0.001**
Laparoscopic assisted (hybrid) LR, no. (%)	5 (1.7)	5 (8.3)	0	0	0	0	**0.001**
Hand-assisted LLR, no. (%)	6 (2.0)	4 (6.7)	0	0	2 (3.3)	0	0.081
Robotic-assisted LLR, no. (%)	28 (9.3)	6 (10.0)	12 (20.0)	6 (10.0)	4 (6.7)	0	**0.005**
Previous abdominal surgery, no. (%)	152 (50.7)	23 (38.3)	26 (43.3)	33 (55.0)	37 (61.7)	33 (55.0)	**0.011**
Previous liver surgery, no. (%)	52 (17.3)	8 (13.3)	8 (13.3)	10 (16.7)	10 (16.7)	16 (26.7)	0.053
ASA score, no. (%) 1 2 3	 13 (4.3) 196 (65.3) 90 (30.3)	 8 (13.3) 47 (78.3) 5 (8.3)	 2 (3.3) 44 (73.3) 14 (23.3)	 1 (1.7) 40 (66.7) 19 (31.7)	 0 37 (61.7) 23 (38.3)	 2 (3.3) 28 (46.7) 30 (50.0)	**<0.001**
Malignant neoplasm, no. (%)	228 (76.0)	46 (76.7)	48 (80.0)	46 (76.7)	47 (78.3)	41 (68.3)	NC
Median (IQR) tumour size, mm	26 (23)	25.0 (22.0)	23.5 (25.0)	25.0 (23.0)	30.0 (30.0)	27.0 (32.0)	0.375
Huge tumours (≥90mm), no. (%)	23 (7.7)	2 (3.3)	3 (5.0)	2 (3.3)	8 (13.3)	8 (13.3)	**0.009**
Multiple tumours, no. (%)	62 (20.7)	9 (15.0)	13 (21.7)	15 (25.0)	13 (21.7)	12 (20.0)	0.546
Concomitant surgery other than cholecystectomy, no. (%)	60 (20.0)	8 (13.3)	10 (16.7)	11 (18.3)	17 (28.3)	14 (23.3)	0.053
Major resection, no. (%)	83 (27.7)	14 (23.3)	17 (28.3)	18 (30.0)	19 (31.7)	15 (25.0)	0.716
Traditional major (>3 segments), no. (%)	49 (16.3)	4 (6.7)	13 (21.7)	10 (16.7)	10 (16.7)	12 (20.0)	0.152
Difficult segments (I, IVa, VII, VIII), no. (%)	131 (43.7)	23 (38.3)	26 (43.3)	27 (45.0)	24 (40.0)	31 (51.7)	0.250
Multiple resections, no. (%)	25 (8.3)	4 (6.7)	6 (10.0)	5 (8.3)	5 (8.3)	5 (8.3)	0.883
Median (IQR) Iwate difficulty score	6 (5)	6 (5)	6.5 (5)	6 (5)	6 (5)	6 (4)	0.684

Table 2. Baseline and outcomes across the 5 groups of 300 consecutive patients who underwent laparoscopic liver resection (Cont'd)

	Total N=300	Group 1 (1–60)	Group 2 (61–120)	Group 3 (121–180)	Group 4 (181–240)	Group 5 (240–300)	*P* value
Iwate difficulty, no. (%)							
Low	59 (19.7)	11 (18.3)	14 (23.3)	11 (18.3)	11 (18.3)	12 (20.0)	0.691
Intermediate	107 (35.7)	22 (36.7)	16 (26.6)	20 (33.3)	22 (36.7)	27 (45.0)	
High	72 (24.0)	15 (25.0)	18 (30.0)	17 (28.3)	15 (25.0)	7 (11.7)	
Expert	62 (20.7)	12 (20.0)	12 (20.0)	12 (20.0)	12 (20.0)	14 (23.3)	
IMM grade, no. (%)							
I, Low	145 (48.3)	29 (48.3)	31 (51.7)	27 (45.0)	28 (46.7)	30 (50.0)	0.524
II, Intermediate	56 (18.7)	13 (21.7)	13 (21.7)	10 (16.7)	11 (18.3)	9 (15.0)	
III, High	99 (33.0)	18 (30.0)	16 (26.7)	23 (38.3)	21 (35.0)	21 (35.0)	
Cirrhosis, no. (%)	77 (25.7)	14 (23.3)	22 (36.7)	11 (18.3)	11 (18.3)	19 (31.7)	0.926
Portal hypertension, no. (%)	18 (6.0)	2 (3.3)	3 (5.0)	1 (1.7)	2 (3.3)	9 (15.7)	**0.010**
Close margins in malignancy ≤1mm, no. (%)	20 (6.7)	0	1 (1.7)	5 (8.3)	3 (5.0)	11 (18.3)	NC
Open conversion, no. (%)	13 (4.3)	6 (10.0)	3 (5.0)	2 (3.3)	0	2 (3.3)	**0.028**
Median (IQR) operating time, min	260 (190)	260.0 (216.0)	230.0 (209.0)	240.0 (215.0)	265.0 (220.0)	270.0 (183.0)	0.756
Median (range) blood loss, mL	200 (450)	300 (510)	250 (575)	100 (350)	175 (250)	150 (344)	**0.028**
Intraoperative blood transfusion, no. (%)	41 (13.7)	14 (23.3)	11 (18.3)	7 (11.7)	4 (6.7)	5 (8.3)	**0.003**
Pringle manoeuvre applied, no. (%)	94 (31.3)	14 (23.3)	19 (31.7)	20 (33.3)	24 (40.0)	17 (28.3)	NC
Median (IQR) postoperative stay, days	4.0 (4.0)	4.0 (3.0)	4.5 (2.0)	4.0 (4.0)	4.0 (4.0)	4.0 (7.0)	0.209
Postoperative morbidity, no. (%)	76 (25.3)	11 (18.3)	14 (23.3)	18 (30.0)	11 (18.3)	22 (36.7)	NC
Morbidity (grade>2)	25 (8.3)	8 (13.3)	3 (5.0)	5 (8.3)	3 (5.0)	6 (10.0)	0.555
Major morbidity (grade 3b–5)	12 (4.0)	5 (8.3)	2 (3.3)	2 (3.3)	1 (1.7)	2 (3.3)	0.145
Reoperation, no. (%)	5 (1.7)	3 (5.0)	0	1 (1.7)	0	1 (1.7)	0.153
30-day mortality, no. (%)	0	0	0	0	0	0	NC
In-hospital mortality, no. (%)	2 (0.7)	0	1 (1.7)	0	1 (1.7)	0	1.000

ASA: American Society of Anesthesiologists; IMM: Institut Mutualiste Montsouris; IQR: interquartile range; LLR: laparoscopic liver resection; LR: liver resection; MIS: minimally invasive surgery; NC: not computable

Table 3. Factors associated with and outcomes of open conversion after laparoscopic liver resection in 300 patients

Factors associated with open conversion	Completed LLR n=287	Open conversion n=13	*P* value	OR (95% CI)	*P* value
Malignant tumour, no. (%)					
Yes	216 (94.7)	12 (5.3)	0.201		
No	71 (98.6)	1 (1.4)			
Surgeon experience, no. (%)					
First 60 cases	54 (90.0)	6 (10.0)	**0.016**	4.04 (1.28–12.80)	**0.017**
Subsequent 240 cases	233 (97.1)	7 (2.9)			
Cirrhosis, no. (%)					
Yes	72 (93.5)	5 (6.5)	0.330		
No	215 (96.4)	8 (3.6)			
Previous abdominal surgery, no. (%)					
Yes	147 (96.7)	5 (3.3)	0.408		
No	140 (94.6)	8 (5.4)			
Previous liver surgery, no. (%)					
Yes	48 (92.3)	4 (7.7)	0.251		
No	239 (96.4)	9 (3.6)			
Concomitant other surgery/ organ resection, no. (%)	57 (95.0)	3 (5.0)	0.728		
Yes	230 (95.8)	10 (4.2)			
No					
ASA score, no. (%)					
3	90 (98.9)	1 (1.1)	0.118		
1/2	197 (94.3)	12 (5.7)			
Portal hypertension, no. (%)					
Yes	17 (94.4)	1 (5.6)	0.560		
No	270 (95.7)	12 (4.3)			
Multifocal tumour, no. (%)					
Yes	59 (95.2)	3 (4.8)	0.736		
No	228 (95.8)	10 (4.2)			
Median (IQR) tumour size, mm	26 (23)	30 (34)	0.558		
Traditional major (≥3 contiguous segments) resection, no. (%)	46 (93.9)	3 (6.1)	0.452		
Yes	241 (96.0)	10 (4.0)			
No					
Major resection, no. (%)					
Yes	78 (94.0)	5 (6.0)	0.358		
No	209 (96.3)	8 (3.7)			
Multiple resections, no. (%)					
Yes	25 (100)	0	0.611		
No	262 (95.3)	13 (4.7)			
Tumour location, no. (%)					
Posterosuperior	124 (94.7)	7 (5.3)	0.449		
Anterolateral	163 (96.4)	6 (3.6)			
Iwate score, no. (%)					
Low/intermediate	162 (97.6)	4 (2.4)	0.088		
High/expert	125 (93.3)	9 (6.7)			
IMM grade					
III, High	91 (91.9)	8 (8.1)	**0.034**	3.74 (1.17–12.00)	**0.026**
I, Low/II, Intermediate	196 (97.5)	5 (2.5)			

Table 3. Factors associated with and outcomes of open conversion after laparoscopic liver resection in 300 patients (Cont'd)

Factors associated with open conversion	Completed LLR n=287	Open conversion n=13	*P* value	OR (95% CI)	*P* value
Outcome of open conversion					
Median (IQR) operation time, min	255 (190)	405 (270)	**0.001**		
Intraoperative blood transfusion, no. (%)					
Yes	31 (10.8)	10 (76.9)	**<0.001**		
No	256 (89.2)	3 (23.1)			
Median (IQR) estimated blood loss, mL	200 (350)	1500 (1250)	**<0.001**		
Median (IQR) postoperative hospitalisation, days	4 (3)	8 (12)	**<0.001**		
Postoperative morbidity, no. (%)					
Yes	65 (22.6)	11 (84.6)	**<0.001**		
No	222 (77.4)	2 (15.4)			
Major morbidity (grade>2), no. (%)					
Yes	21 (7.3)	9 (69.2)	**0.021**		
No	266 (92.7)	4 (30.8)			
Mortality, no. (%)					
30-day	0	0	1.000		
In-hospital	2 (0.7)	0			

ASA: American Society of Anesthesiologists; CI: confidence interval; IMM: Institut Mutualiste Montsouris; IQR: interquartile range; LLR: laparoscopic liver resection; OR: odds ratio

assistance) can be used for haemostasis depending on the situation.[33] It is important to highlight that surgeons should be prepared to convert early if deemed necessary, especially during their early experience, as this may potentially reduce blood loss and postoperative morbidity.[35]

Due to its retrospective nature, there are various limitations associated with the current study. As previously highlighted,[18] it is important to emphasise that the surgeon's experience in this study is unique and may not be directly translated to that of other surgeons embarking on LLR. Firstly, the surgeon had a vast prior experience with open and complex hepatopancreatobiliary surgeries, including transplantation before embarking on LLR. Secondly, although the surgeon had no formal training and prior exposure to LLR, he had extensive experience in other complex laparoscopic procedures such as donor nephrectomies. Thirdly, during the study period, the surgeon had also gained further laparoscopic experience by performing other abdominal procedures such as pancreatectomies, gastric resections and major biliary procedures.[7,36] Fourthly, as the surgeon was practising in a high-volume centre, he had gained further concomitant experience with LLR by tutoring and assisting other surgeons who were adopting LLR during the study period. Finally, it is also important to add that the learning curve of a surgeon exposed to LLR, such as an LLR fellowship-trained surgeon, would likely be shorter and less steep than the current reported experience.

In conclusion, this study based on a single surgeon's experience demonstrates that LLR can be safely adopted for resections of all difficulty grades, including major resections and resection of tumours located in the difficult posterosuperior segments with a low open conversion rate. Surgeon experience and IMM high grade resections were significant factors associated with open conversion.

Disclosure

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REFERENCES

1. Goh BK, Teo RY. Current status of laparoscopic and robotic pancreatic surgery and its adoption in Singapore. Ann Acad Med Singap 2020;49:377-83.
2. Reich H, McGlynn F, DeCaprio J, et al. Laparoscopic excision of benign liver lesions. Obstet Gynecol 1991;78:956-8.

3. Gagner M, Rheault M, Dubuc J. Laparoscopic partial hepatectomy for liver tumor. Abstracts of the 1992 scientific session of the Society of American Gastrointestinal Surgeons (SAGES), Washington DC, USA. 1992:85-110.
4. Vigano L, Laurent A, Tayar C, et al. The learning curve in laparoscopic liver resection: improved feasibility and reproducibility. Ann Surg 2009;250:772-82.
5. Hasegawa Y, Nitta H, Takahara T, et al. Safely extending the indications of laparoscopic liver resection: when should we start laparoscopic major hepatectomy? Surg Endosc 2017;31:309-16.
6. Tomassini F, Scuderi V, Colman R, et al. The single surgeon learning curve of laparoscopic liver resection. A continuous evolving process through stepwise difficulties. Medicine (Baltimore) 2016;95:e5138.
7. Goh BK, Low TY, Teo JY, et al. Adoption of robotic liver, pancreatic and biliary surgery in Singapore: a single institution experience with its first 100 consecutive cases. Ann Acad Med Singap 2020;49:742-8.
8. Syn N, Kabir T, Koh YX, et al. Survival advantage of laparoscopic versus open resection for colorectal liver metastases: a meta-analysis of individual patient data from randomized trials and propensity-score matched studies. Ann Surg 2020;272:253-65.
9. Chang SK, Tay CW, Shen L, et al. Long-term oncological safety of minimally invasive hepatectomy in patients with hepatocellular carcinoma: a case-control study. Ann Acad Med Singap 2016;45:91-7.
10. Ciria R, Cherqui D, Geller DA, et al. Comparative short-term benefits of laparoscopic liver resection: 9000 cases and climbing. Ann Surg 2016;263:761-77.
11. Aghayan DL, Kazaryan AM, Fretland ÅA, et al. Evolution of laparoscopic liver surgery: 20-year experience of a Norwegian high-volume referral center. Surg Endosc 2021. doi:10.1007/s00464-021-08570-3.
12. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 2015;261:619-29.
13. Buell JF, Cherqui D, Geller DA, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. Ann Surg 2009;250:825-30.
14. Abu Hilal M, Aldrighetti L, Dagher I, et al. The Southampton consensus guidelines for laparoscopic liver surgery: From indication to implementation. Ann Surg 2018;268:11-8.
15. Tan CH, Tan KH, Lee CL, et al. Observing an upward trajectory in minimally invasive hepatectomies in Singapore—a nationwide analysis. Ann Laparosc Endosc Surg 2018;3:78.
16. Goh BKP, Lee SY, Teo JY, et al. Changing trends and outcomes associated with the adoption of minimally invasive hepatectomy: a contemporary single-institution experience with 400 consecutive resections. Surg Endosc 2018;32:4658-65.
17. Goh BK, Teo JY, Chan CY, et al. Evolution of laparoscopic liver resection at Singapore General Hospital: a nine-year experience of 195 consecutive resections. Singapore Med J 2017;58:708-13.
18. Goh BKP, Prieto M, Syn N, et al. Critical appraisal of the learning curve of minimally-invasive hepatectomy: experience with the first 200 cases of a Southeast Asian early adopter. ANZ J Surg 2020; 90:1092-98.
19. Mohan R, Kabir T, Wu AGR, et al. Analysis of perioperative outcomes following laparoscopic repeat liver resection compared to laparoscopic primary liver resection based on a single surgeon's experience: a 1:2 propensity score-matched study. Surg Oncol 2020;35:382-7.
20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.
21. Strasberg SM. Nomenclature of hepatic anatomy and resection: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg 2005;12:351-5.
22. Hwang DM, Han HS, Yoon YS, et al. Laparoscopic major liver resection in Korea: a multicenter study. J Hepatobiliary Pancreat Sci 2013;20:125-30.
23. Wakabayashi G. What has changed after the Morioka consensus conference 2014 on laparoscopic liver resection. Hepatobiliary Surg Nutr 2016;5:281-9.
24. Kawaguchi Y, Fuks D, Kokudo N, et al. Difficulty of laparoscopic liver resection: proposal for a new classification. Ann Surg 2018;267:13-7.
25. Komatsu S, Scatton O, Goumard C, et al. Development process and technical aspects of laparoscopic hepatectomy: learning curve based on 15 years experience. J Am Coll Surg 2017;224:841-50.
26. Nomi T, Fuks D, Kawaguchi Y, et al. Learning curve for laparoscopic major hepatectomy. Br J Surg 2015;102:796-804.
27. Halls MC, Alseidi A, Berardi G, et al. A comparison of the learning curves of laparoscopic liver surgeons in differing stages of the IDEAL paradigm of surgical innovation. Ann Surg 2019;269:221-8.
28. Chua D, Syn N, Koh YX, et al. Learning curves in minimally invasive hepatectomy: systematic review and meta-regression analysis. Br J Surg 2021;108:351-8.
29. Goh BKP, Prieto M, Syn N, et al. Validation and comparison of the Iwate, IMM, Southampton and Hasegawa difficulty scoring systems for primary laparoscopic hepatectomies. HPB (Oxford) 2021;23:770-6.
30. Goh BKP, Lee SY, Koh YX, et al. Minimally invasive major hepatectomies: a Southeast Asia single institution contemporary experience with its first 120 consecutive cases. ANZ J Surg 2020;90:553-7.
31. Goh BK, Syn N, Lee SY, et al. Impact of liver cirrhosis on the difficulty of minimally-invasive liver resections: a 1:1 coarsened exact-matched controlled study. Surg Endosc 2021;35:5231-8.
32. Kabir T, Syn NL, Guo Y, et al. Laparoscopic liver resection for huge (≥10cm) hepatocellular carcinoma: A coarsened exact-matched single-surgeon study. Surg Oncol 2021;37:101569.
33. Goh BK, Chan CY, Wong JS, et al. Factors associated with and outcomes of open conversion after laparoscopic minor hepatectomy. Surg Endosc 2015;29:2636-42.
34. Troisi RI, Montalti R, Van Limmen JG, et al. Risk factors and management of conversions to an open approach in laparoscopic liver resection: analysis of 265 consecutive cases. HPB (Oxford) 2014;16:75-82.
35. Costi R, Scatton O, Haddad L, et al. Lessons learned from the first 100 laparoscopic liver resections: not delaying conversion may allow reduced blood loss and operative time. J Laparoendosc Adv Surg Tech A 2012;22:425-31.
36. Goh BKP, Zeng G, Low TY, et al. Changing trends and outcomes associated with the adoption of minimally-invasive pancreato-biliary surgery: contemporary experience of a 'self-taught' early adopter in Southeast Asia. J Minim Access Surg 2020;16:341-7.

ORIGINAL ARTICLE

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Factors and experiences associated with unscheduled 30-day hospital readmission: A mixed method study

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ABSTRACT

Introduction: Analysis of risk factors can pave the way for reducing unscheduled hospital readmissions and improve resource utilisation.

Methods: This was a concurrent nested, mixed method study. Factors associated with patients readmitted within 30 days between 2011 and 2015 at the National University Hospital, Singapore (N=104,496) were examined. Fifty patients were sampled in 2016 to inform an embedded qualitative study. Narrative interviews explored the periods of readmissions and related experiences, contrasted against those of non-readmitted patients.

Results: Neoplastic disease (odds ratio [OR] 1.91, 95% confidence interval [CI] 1.70–2.15), number of discharged medications (5 to 10 medications OR 1.21, 95% CI 1.14–1.29; ≥11 medications OR 1.80, 95% CI 1.66–1.95) and length of stay >7 days (OR 1.46, 95% CI 1.36–1.58) were most significantly associated with readmissions. Other factors including number of surgical operations, subvention class, number of emergency department visits in the previous year, hospital bill size, gender, age, Charlson comorbidity index and ethnicity were also independently associated with hospital readmissions. Although readmitted and non-readmitted patients shared some common experiences, they reported different psychological reactions to their illnesses and viewed hospital care differently. Negative emotions, feeling of being left out by the healthcare team and perception of ineffective or inappropriate treatment were expressed by readmitted patients.

Conclusion: Patient, hospital and system-related factors were associated with readmissions, which may allow early identification of at-risk patients. Qualitative analysis suggested several areas of improvement in care including greater empowerment and involvement of patients in care and decision making.

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Keywords: Comorbidity, diagnosis, hospital readmission, qualitative evaluation, socioeconomic factors

INTRODUCTION

Readmission leads to a greater demand for healthcare services, especially hospital beds, and contributes to the rising healthcare costs.[1,2] With estimated one-third of the readmissions considered preventable,[3] early identification of the underlying risk factors can offer better management and discharge planning.[4] Some risk factors of readmissions related to patient (e.g. age, comorbidities) and hospital (e.g. bed occupancy rate, discharge destination) may be common in different geographical regions; however, many factors including socioeconomic conditions are unique to specific areas. Asian studies are largely limited to elderly patients[5] or specific conditions.[6,7] In 2019, the 30-day unplanned readmission rate in Singapore was 18.6% among patients aged 65 years and older.[8] Singapore's national and institutional targets were less than 10% and 11.37%, respectively.

Risk models have been developed using large administrative databases to predict 30-day hospital readmission such as the LACE (L: length of hospital

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CLINICAL IMPACT

What is New

- This study highlights the importance of both quantitative (patient, hospital, and system-related characteristics) and qualitative (patients' experience) factors associated with hospital readmissions.
- The study covered a general adult hospitalised cohort including surgical patients.

Clinical Implications

- Early identification of patients with potential risk factors will reduce hospital readmissions.
- The findings support the need in empowering patients and involving them in decision-making on their health matters and disease management.

stay; A: acuity on admission; C: comorbidity; E: emergency department visits) index,[9] HOSPITAL score (H: haemoglobin; O: discharge from an *o*ncology service; S: sodium level at discharge; P: procedure during the index admission; I and T: index type of admission [non-elective versus elective]; A: number of admissions during the past 12 months; L: length of stay),[10] and risk prediction model.[11] These models have limited number of variables, which are attractive for administration purposes but have reduced prediction ability (area under curve 0.68–0.71). Indeed, a systematic review that included 26 different risk prediction models concluded that most performed poorly.[11] Social, environmental, and post-discharge factors contributing significantly to hospital readmissions are not captured in administrative data, and therefore not studied adequately.[11]

Readmitted patients have revealed consistent themes of post-hospital vulnerability.[12-14] A qualitative study[12] exploring readmissions among diabetic patients identified several themes that contributed to the readmission risk, including poor health literacy, lack of awareness of medication changes, and post-discharge support. Most of the patients required help with transportation, medications and food, and generally believed that being readmitted was out of their control.[12] Older readmitted patients were often uninformed about their own care and at times felt unheard and ignored by the healthcare professionals. In some instances, patients affirmed their feelings of not being fully recovered or well enough to go home.[15]

Application of mixed methodology with concurrent analysis of quantitative and qualitative data is likely to improve the understanding of the complex issues associated with readmission but uncommon in literature for general patient population. Our main objective was to identify factors associated with 30-day unscheduled hospital readmission by analysing a large administrative database. We also explored the question of how such experiences were lived, comparing the readmitted and the non-readmitted and cataloguing similarities and differences, in an embedded qualitative study.

METHODS

The study was conducted at the National University Hospital, Singapore—a 1,200-bed university-affiliated hospital. We adopted a concurrent nested mixed method design.[16,17] By using both methods, we were able to exploit the strengths of each (quantifying what is known) while redressing inherent weaknesses (qualifying lived experiences and new potential explanations). The study was approved by the National Healthcare Group Domain Specific Review Board (Reference no: 2016/00339). The respective quantitative and qualitative methodologies are described below.

Quantitative methods

Administrative hospital data involving several systems, including the registration, electronic health records and pharmacy databases, were extracted between January 2011 and December 2015. The sample selection of the quantitative study is shown in Fig. 1. It consisted of inpatients aged ≥18 years at the time of index admission and survived to hospital discharge. We considered patients with first admission during the study period and excluded those whose "first admission" was a readmission from the previous 30 days from 31 December 2010. Using rule of 10 outcome events for each predictor variable tested in a logistic regression model,[18] the study was sufficiently powered to identify factors associated with readmissions for 104,496 patients.

The administrative data consisted of demographics, discharge status (home or step-down care), subvention category (as a marker of socioeconomic status), diagnoses, comorbidities using Charlson comorbidity index (CCI), surgical operations during the index admission, discharge medications, hospital length of stay (LOS), number of emergency department visits in the past 12 months from the day of index admission, and hospital bill size (before subvention). Age was divided into 4 categories: 18–29, 30–49, 50–69 and ≥70 years.

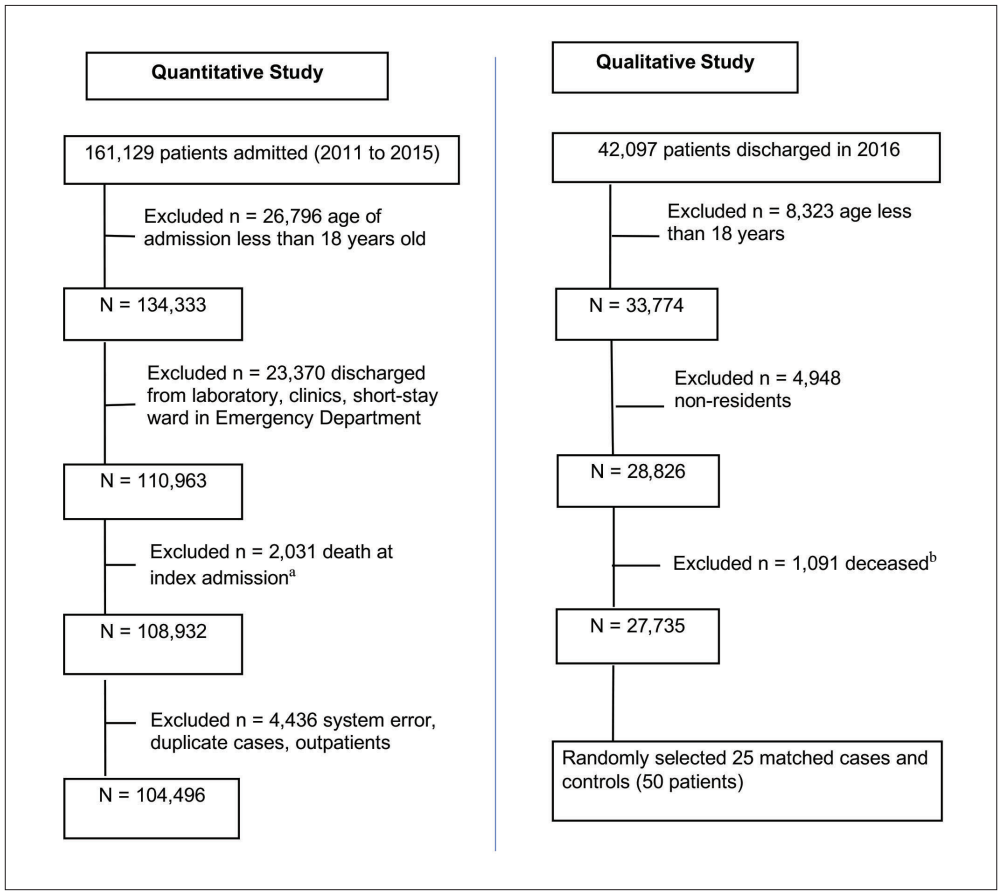

Fig. 1. Schematic diagram of patients included in the respective studies.

[a] Patients who died during the index admission (n=2,031) were excluded as they had only one admission during the study period and passed away in that admission.

[b] All the death cases in 2016 (n=1,091) were excluded from the qualitative study.

Number of surgical operations was grouped as 0, 1, 2 and ≥3. Length of stay was grouped as 1–7 and >7 days. Diagnosis was grouped into 11 broad disease categories: circulatory system, injury/poisoning/external causes of disease, pregnancy/childbirth/puerperium-related, neoplasms/haemopoietic system, digestive system, respiratory system, genitourinary system, nervous system, endocrine/metabolic system, eye/ear disease and others. There were no missing values for all the quantitative variables except number of discharged medications, which had 4.1% missing value due to incomplete records.

Statistical methods

The characteristics of patients with and without readmissions were compared using chi-square test. Multivariable logistic regression was carried out to identify factors that were associated with 30-day readmission. Variables or a surrogate thereof that have been shown to predict readmission after extensive literature search,[9-11] as well as additional variables in the database that were found to be significant at the 5% level in the bivariate analysis were considered for inclusion in the multivariable analysis. The effect of risk factors was quantified based on the odds ratio (OR) estimate and its associated 95% confidence interval (CI). The likelihood ratio statistics was used as a measure of importance amongst significant predictors in the multivariable model. The quantitative statistical analyses were conducted using Stata version 15 (StataCorp, College Station, US). All tests were two-sided, with a P value <0.05 considered as statistically significant.

Qualitative methods

The qualitative phase of the study was conducted from January to December 2016; it is described following the consolidated criteria for reporting qualitative studies.[19]

Research team reflexivity

Qualitative data were collected by team members working as public health practitioners, who are familiar with English and local languages in Singapore

(Mandarin, Malay or Tamil). Rapport was built over a first telephone contact and during one meeting, and by adjusting for language preferences.

Theoretical framework

A phenomenological approach was used,[20] with the emphasis on contrasting lived experiences of readmission within 30 days against single admissions. A comparative thematic analysis was employed to highlight similarities and differences between these groups that were anchored onto topics of interest, as described below.

Participant selection

The qualitative sample was extracted from a list of patients admitted in 2016, ranking from the most common to least common diagnoses, and classifying them as readmitted or non-readmitted patients within 30 days. Patients were matched by gender, age, ethnicity and primary discharge diagnosis and selected using maximum variation sampling (Table 1). Twenty-five such matched pairs consented to participate. Following obtaining permission from the attending physicians, shortlisted candidates were contacted by letter. Patients were then followed up by telephone and invited to take part in a face-to-face interview with one or 2 interviewers.

Setting and sample

A total of 86 participants were identified to take part in the study; 34 refused and attending physicians did not agree for 2 patients to be approached. Interviews took place in setting most convenient to the participant, most frequently in a private area at the hospital (45 patients). A handful of interviews took place in the participant's house (5 patients). On 2 occasions, family members and caregivers were present at the patient's request.

Data collection

Following informed consent, the interviews were conducted using a semi-structured topic guide, which allowed the interviewers to move between the topics. These were related to exploring (1) first admission and readmissions, (2) length of stay, (3) disease progression, (4) medication, (5) discharge instructions and self-care, (6) social support or lack thereof, and (7) emotional highs and lows. The guide was matched to the study objectives and successfully piloted prior to use (Table 2).

Interviews were recorded, transcribed verbatim and translated into English (when the medium was a different language). Interviews lasted half-an-hour to an hour, and saturation on broad explanatory themes began to emerge about halfway through the scheduled 50 interviews. Repeat interviews were not carried out.

Data analysis and reporting

Framework analysis was employed.[21] Researchers familiarised themselves with the data to see if new topics emerged beyond those selected a priori, according to the topics in the interview guide as outlined above; none did. Data were then indexed and organised according to topics using NVivo 11.0 (QSR International, Burlington, US) data management software. Organised data were subsequently charted into an Excel matrix, according to the agreed topics. Line-by-line coding was then applied within the framework, allowing explanatory shared themes to be identified and contrasted between the readmitted and non-readmitted groups. Thematic analysis is reported using illustrative quotes.[22] All data were double coded, and there were no major discrepancies between coders. Interpretations and minor differences in coding were discussed, and a consensus reached on the meaning of the data.

RESULTS

Quantitative study

Table 3 shows the patient characteristics and factors affecting 30-day readmission. Out of 104,496 patients, one-third was aged 30–49 (31.2%) and another one-third 50–69 (32.2%) years, with readmission rising significantly with increasing age. Majority of the patients were ethnic Chinese (57.6%), male and received subsidised care. Other factors that were significantly associated with increased risk of readmission included: discharge destination, increased number of medications upon discharge, and longer inpatient LOS.

Apart from discharge destination, all other factors identified as predictors of 30-day readmission in the bivariate analysis remained significant in the multivariable analysis (Table 4). The strongest predictors of readmission were speciality diagnosis, increased number of medications upon discharge, hospital LOS>7 days and subvention class. The odds of readmission were the highest among patients with haematology-oncological malignancy (OR 1.91, 95% CI 1.70–2.15) as compared to pregnancy, childbirth and puerperium. Although surgical patients had reduced risk of readmission compared to medical patients, the odds of readmission rates increased (0.55–0.80) with higher number of surgical procedures during the index admission. Older age, higher CCI, male sex, higher hospital bill size and Malay ethnicity were also

Table 1. Patient selection for the qualitative study

		Readmitted (n=25) No. (%)	Non-readmitted (n=25) No. (%)
Sex	Male	14 (56)	14 (56)
	Female	11 (44)	11 (44)
Age, years	19–29	2 (8)	1 (4)
	30–49	4 (16)	5 (20)
	50–69	13 (52)	12 (48)
	70 and above	6 (24)	7 (28)
Ethnicity	Chinese	16 (64)	15 (60)
	Malay	5 (20)	6 (24)
	Indian	2 (8)	3 (12)
	Others	2 (8)	1 (4)
Diseases	Heart disease (congestive heart failure, chest pain, acute myocardial infarction and atherosclerotic heart disease)	6 (24)	7 (28)
	Respiratory disease (pneumonia and COPD)	4 (16)	4 (16)
	Cancer (malignant neoplasm of ovary, secondary malignant neoplasm of liver, lymphoma)	3 (12)	1 (4)
	Urinary tract infection	1 (4)	2 (8)
	Cellulitis	1 (4)	1 (4)
	Chronic kidney disease	1 (4)	1 (4)
	Gout	1 (4)	1 (4)
	Diabetes mellitus	1 (4)	1 (4)
	Complications of cardiac and vascular prosthetic devices, implants and grafts	1 (4)	1 (4)
	Thyroid nodule, goitre	1 (4)	1 (4)
	Cholecystitis and wound infection following a procedure	1 (4)	1 (4)
	Constipation colic	1 (4)	1 (4)
	Rheumatoid arthritis	1 (4)	1 (4)
	Sleep apnoea	1 (4)	1 (4)
	Haemorrhage and haematoma complicating a procedure	1 (4)	1 (4)

COPD: chronic obstructive pulmonary disease
Fifty patients (25 pairs) were selected for the interview from the readmitted cases in 2016.
In the first stage, age was stratified into 4 groups. The number of pairs of patients needed in each age category was proportional to the total number of patients in each age category in order to represent all ages.
In the second stage, the number of pairs of patients needed in gender was proportionated.
In the last stage, the number of pairs of patients needed in each ethnic group was proportionated in order to represent the ethnic proportions of Chinese, Malay, Indian and others

Table 2. Topic guide with illustrative questions and prompts

Topics	Questions and prompts
1a. Could you tell me about your first admission to the hospital in 2016?	Why and how did this admission occurred? – *Please explain about your first admission*
1b. Could you tell me about your readmission to the hospital? [if applicable]	Could you tell me why you think you are so frequently readmitted? – *Who made the decision to return to the hospital? (doctor, caregiver, patient)* – *Was there anything you did or did not do that led to readmission?* – *Do you think you did anything that may have made your condition worse?* – *Could you tell me what might have helped prevent having to be readmitted?*
2. Length of stay	How many days did you stay in hospital [each time you were admitted as applicable]? – *Can you explain more about this experience?*
3. Disease progression	When was the disease first diagnosed? – *Can you tell me about living with this disease being present?*
4. Medications	What medication are you taking? – *Can you explain about the instruction that the doctor gave you for taking them?* – *Do you take your medications as directed by your physician? Why / why not?* – *Did you have any specific problems in being able to obtain the medications that you need? If so, tell me about it.*
5. Discharge instructions and self-care	Please tell me what you remember from your discharge instructions – *How was it overall? What happened?* – *What arrangements were made for you when you went home?* – *Did you follow all of the discharge instructions? If not, then why?* – *Did you feel able to care for yourself after discharge? Can you tell me why or why not?* – *Were you specifically financially able to do so? Please explain your answer.* – *Can you tell me what you know about taking care of yourself with your current condition; including healthy dieting?*
6. Social support/or lack thereof	Tell me about your social support at home. – *Did you have proper support once you left the hospital? Can you tell me more about this?* – *Did you have any questions about how to care for yourself? How were you able to get the questions answered?*
7. Emotional high/lows	How do you feel after discharged home? – *Please explain your feelings.* How do you feel about staying in hospital? – *What was difficult about it?* – *What types of things might have made the experience good, or even better?*

associated with increased readmission rates, in decreasing order of significance.

Qualitative study results

In the qualitative study, themes are summarised in Table 5 alongside illustrative quotes. Some repeated themes emerged as frequently shared across both the non-readmitted and the readmitted patients; others were unique to each group. Both groups generally expressed that they had adequate home support after discharge; although the participants in the non-readmitted group imparted a stronger sense of self-efficacy, for example by suggesting that they were prepared and able to take care of themselves after discharge—such statements did not emerge from the readmitted patients' accounts. Having adequate financial resources to access health services was also mostly expressed as a shared experience, although some readmitted patients mentioned lack of resources as a reason for missing medical follow-ups. Proper discharge instructions were often reported to be given to both groups; while reporting compliance to medical appointments, but less so to medication, was also an experience that was equally shared across both groups. In both groups, patients who admitted non-adherence said they did so because they were too busy or that they simply forgot.

On the other hand, the readmitted group reported having more negative emotions related to the patient role; or feeling powerless and hopeless over their condition. They also reported feeling like a burden in the wards and "left out" of care and treatment decisions. A repeated, dominant theme was also identified in this group around feeling that the wrong medicine or ineffective treatment was being given. These

Table 3. Patient characteristics by readmission status

Factors		Readmission within 30 days	
	Total (N=104,496)	Readmitted (n=8,982)	Non-readmitted (n=95,514)
Age years, no. (%)[a]			
18–29	18,818 (18.0)	991 (11.03)	17,827 (18.66)
30–49	32,608 (31.2)	2,074 (23.09)	30,534 (31.97)
50–69	33,695 (32.2)	3,494 (38.90)	30,201 (31.62)
≥70	19,375 (18.5)	2,423 (26.98)	16,952 (17.75)
Sex, no. (%)[a]			
Male	51,867 (49.6)	4,694 (52.3)	47,173 (49.4)
Female	52,629 (50.4)	4,288 (47.7)	48,341 (50.6)
Ethnicity, no. (%)[a]			
Chinese	60,168 (57.6)	5,481 (61.0)	54,687 (57.3)
Indian	13,388 (12.8)	893 (9.9)	12,495 (13.1)
Malay	14,746 (14.1)	1,401 (15.6)	13,345 (14.0)
Others	16,194 (15.5)	1,207 (13.4)	14,987 (15.7)
Patient class, no. (%)[a]			
Private	41,014 (39.3)	2,528 (28.2)	38,486 (40.3)
Subsidised	63,482 (60.8)	6,454 (71.9)	57,028 (59.7)
Discharge destination, no. (%)[a]			
Home	99,205 (94.9)	8,341 (92.9)	90,864 (95.1)
Stepdown care facility	5,291 (5.1)	641 (7.1)	4,650 (4.9)
Number of surgical operation, no. (%)[a]			
0	52,098 (49.9)	4,998 (55.6)	47,100 (49.3)
1	43,127 (41.3)	2,765 (30.8)	40,362 (42.3)
2	6,302 (6.0)	778 (8.7)	5,524 (5.8)
≥3	2,969 (2.8)	441 (4.9)	2,528 (2.7)
Length of stay, days, no. (%)[a]			
1–7	86,984 (83.2)	6,272 (69.8)	80,712 (84.5)
>7	17,512 (16.8)	2,710 (30.2)	14,802 (15.5)
Number of discharge medication, no. (%)[a,b]			
0–4	39,615 (39.5)	2,196 (26.0)	37,419 (40.8)
5–10	46,970 (46.9)	4,027 (47.7)	42,943 (46.8)
≥11	13,668 (13.6)	2,225 (26.3)	11,443 (12.5)
Charlson Comorbidity Index, no. (%)[a]			
0–3	83,355 (79.8)	5,696 (63.4)	77,659 (81.3)
4–7	17,681 (16.9)	2,529 (28.2)	15,152 (15.9)
≥8	3,460 (3.3)	757 (8.4)	2,703 (2.8)

Table 3. Patient characteristics by readmission status (Cont'd)

Factors	Readmission within 30 days		
	Total (N=104,496)	Readmitted (n=8,982)	Non-readmitted (n=95,514)
Number of visit to emergency department in past 12 months, no. (%)[a]			
0	27,707 (26.5)	2,628 (29.3)	25,079 (26.3)
1	64,781 (62.0)	5,195 (57.8)	59,586 (62.3)
2	9,184 (8.8)	889 (9.9)	8,295 (8.7)
3	1,885 (1.8)	186 (2.1)	1,699 (1.8)
≥4	939 (0.9)	84 (0.9)	855 (0.9)
Hospital bill, SGD, no. (%)			
<2,000	25,049 (24.0)	1,942 (21.6)	23,107 (24.2)
2,000 to <4,000	23,613 (22.6)	1,603 (17.8)	22,010 (23.0)
4,000 to <6,000	16,107 (15.4)	1,138 (12.7)	14,969 (15.7)
6,000 to <8,000	9,916 (9.5)	729 (8.1)	9.187 (9.6)
8,000 to <10,000	5,819 (5.6)	551 (6.1)	5,268 (5.5)
≥10,000	23,992 (23.0)	3,019 (33.6)	20,973 (22.0)
Diagnosis groups, no. (%)[a]			
Others	21,920 (21.0)	1,369 (15.2)	20,551 (21.5)
Circulatory system	15,446 (14.8)	1,826 (20.3)	13,620 (14.3)
Injury, poisoning and external causes	14,699 (14.1)	758 (8.4)	13.941 (14.6)
Pregnancy, childbirth and puerperium	13,065 (12.5)	830 (9.2)	12,235 (12.8)
Neoplasms and diseases of blood	9,763 (9.3)	1,923 (21.4)	7.840 (8.2)
Digestive system	8,947 (8.6)	716 (8.0)	8,231 (8.6)
Respiratory system	6,470 (6.2)	490 (5.5)	5,980 (6.3)
Genitourinary system	5,287 (5.1)	384 (4.3)	4,903 (5.1)
Nervous system	3,921 (3.8)	277 (3.1)	3,644 (3.8)
Endocrine and metabolic diseases	3,469 (3.3)	358 (4.0)	3,111 (3.3)
Eye, adnexa, ear and mastoid process	1,509 (1.4)	51 (0.6)	1,458 (1.5)

SGD: Singapore dollar [a]
Significant at $P<0.001$
[b] Information available for only 100,253 patients

patients shared their frustration that the medication given took a long time to take effect, which may have contributed to non-compliance. The readmitters also often described having less knowledge and/or compliance to healthy diet.

DISCUSSION

Our study highlighted that hospital readmission is a complex process with a wide range of contributing factors. Disease category was the highest risk factor of readmission. Increasing age and number of

Table 4. Significant predictors of 30-day readmission in the multivariable logistic regression

Characteristics	Subgroup	Adjusted 30-day readmission rate OR (95% CI)
Diagnosis groups	Pregnancy, childbirth and puerperium	Ref
	Neoplasms and diseases of blood	1.91 (1.70–2.15)[a]
	Digestive system	0.84 (0.74–0.96)[a]
	Circulatory system	0.83 (0.73–0.93)[a]
	Endocrine and metabolic diseases	0.70 (0.60–0.81)[a]
	Genitourinary system	0.65 (0.56–0.76)[a]
	Nervous system	0.52 (0.44–0.62)[a]
	Others	0.51 (0.45–0.57)[a]
	Respiratory system	0.50 (0.43–0.58)[a]
	Injury, poisoning and external causes	0.46 (0.41–0.53)[a]
	Eye, adnexa, ear and mastoid process	0.28 (0.21–0.38)[a]
Number of discharge medication	0–4	Ref
	5–10	1.21 (1.14–1.29)[a]
	≥11	1.80 (1.66–1.95)[a]
Length of stay, days	1–7	1.00
	>7	1.46 (1.36–1.58)[a]
Patient class	Private	Ref
	Subsidised	1.42 (1.34–1.51)[a]
Age group, years	18–29	Ref
	30–49	1.12 (1.02–1.22)[a]
	50–69	1.35 (1.23–1.48)[a]
	≥70	1.43 (1.29–1.58)[a]
Number of visits to emergency department in past 12 months	0	Ref
	1	0.91 (0.85–0.97)[a]
	2	1.22 (1.11–1.34)[a]
	3	1.35 (1.13–1.60)[a]
	≥4	1.31 (1.02–1.66)[a]
Charlson Comorbidity Index	0–3	Ref
	4–7	1.25 (1.17–1.32)[a]
	≥8	1.29 (1.16–1.43)[a]
Hospital bill, SGD	<2,000	Ref
	2,000 to <4,000	0.96 (0.89–1.04)
	4,000 to <6,000	1.04 (0.95–1.13)
	6,000 to <8,000	0.98 (0.88–1.09)
	8,000 to <10,000	1.17 (1.04–1.32)[a]
	≥10,000	1.18 (1.06–1.32)[a]

Table 4. Significant predictors of 30-day readmission in the multivariable logistic regression (Cont'd)

Characteristics	Subgroup	Adjusted 30-day readmission rate OR (95% CI)
Ethnicity	Chinese	Ref
	Indian	0.95 (0.88–1.04)
	Malay	1.10 (1.03–1.18)[a]
	Others	1.04 (0.97–1.13)
Sex	Female	Ref
	Male	1.17 (1.12–1.23)[a]
Number of surgical operations	0	Ref
	1	0.55 (0.51–0.58)[a]
	2	0.74 (0.67–0.82)[a]
	≥3	0.80 (0.71–0.91)[a]

CI: confidence interval; OR: odds ratio; Ref: reference; SGD: Singapore dollar
[a] Significant at $P<0.05$

comorbidities can be related but also predicted readmissions independently. Similarly, number of medications used and frequent visits to the emergency department are markers of disease burden and high healthcare utilisation, respectively, which were independently associated with readmission. Patients destined for readmission had longer LOS and higher hospital bill size, therefore likely opted for government subvention during their index admissions.

Some of the risk factors in our study are common with the previous literature. In the HOSPITAL score study, LOS during the index admission and discharge from oncological services were associated with higher risks of readmission,[10] which was similar to our investigation. We found that the number of emergency department visits in preceding 12 months was associated with readmission while Donze et al. established that the number of inpatient hospital admissions during similar duration was predictive.[10] LACE index also included variables like LOS, CCI and emergency visit in previous 6 months, which was consistent with our study.[9] However, we identified additional factors including age, medical versus surgical admissions, number of operations and number of discharge medications to be also independently associated with readmission.

One important aspect of the current study is the inclusion of qualitative data from patients' interviews. Analyses revealed shared experiences of medicine adherence, self-care upon discharge, and social support by admitted and readmitted patients. Overall, finances were often not a barrier to care-seeking for either. Notable and emphatic differences between patient accounts were around their hospitalisation experiences, and respective positive versus negative internalisation of the "patient role" (i.e. self-efficacy in recovery versus feeling like a burden). This negative self-concept appeared in turn to be connected to readmitted patients' feeling of being less involved in their treatment, decision-making and that the "wrong" treatment was being administered. This narrative suggests a profile of readmitted patients that fits with more complex medical cases, and those undergoing multiple operations, overlapping with a lack of empowerment to participate in treatment options. Our qualitative analysis suggests a complex set of dynamics that underpins the clinical assumptions around adherence and clinical follow-through after discharge.

During the interpretation stage of the mixed methodology of the project, we find integration in the quantitative outcomes and qualitative experience of the patients. The quantitative data identify patients with chronic diseases (cardiovascular, respiratory and endocrine-related diseases) to have higher odds of readmissions. Typical markers of chronic disease population include elderly age, frequent emergency department visits, longer LOS and increased number of discharge medications. It is understandable that some of these patients feel frustrated and believe that medications are either not working or wrongly given. Similar findings were observed in a qualitative study of elderly patients readmitted to an Australian hospital who expressed feeling of neglect in care, lack of knowledge-sharing and being given mixed messages in relation to the outcome.[15] During the interview, readmitted patients expressed inability to control their

Table 5. Themes and subthemes explaining readmission in the qualitative study

Theme	Shared theme[a]	Illustrative quotes from readmitted patients	Illustrative quotes from non-readmitted patients
Social support			
Adequate home support	✓	"My daughter helps me with the dressing and everything… only my daughter takes care of me… and though she is working… and she's busy with two kids… but yet she really cares for me." (041, female, 62 years old) "My son is a doctor who's staying just a block in front of my house. So, he visits me very frequently. His maid will come over and help me clean my house." (023, female,78 years old)	"After I discharge… at the beginning that few days [sic], it was my husband and my younger brother like […] They took turns to take care of me…" (062, female, 42 years old) "My daughter-in-law… she has been taking care of me…cooking or anything also she do... any housework also she help to do…" (006, female, 74 years old)
Self-reliance/self-efficacy			
Prepared and feeling able to take care of themselves after discharge (self-efficacy)	X	NA	"I don't need him to take care of me. I can take care of myself." (044, female, 68 years old) "I am able to take care of myself." (040, female, 55 years old)"
Finances			
Reports of having adequate financial resources	✓	"Because I am…under pension, so everything still okay...No problem for the medicine from the hospital, [this is given] under pension. I pay only 50 cents so quite all right, quite okay." (017, male, 81 years old) "Financial not really an issue." (003, male, 40 years old)	"Because I have the pioneer generation card privileges, so I got some subsidy from it, also deduct from the CPF [so financial issues are] still okay." (006, female, 74 years old) "My company pay for it…then I not worried about that…" (046, male, 56 years old)
Compliance			
Compliant to medical appointments, but less so to medication	✓	"Sometimes I do forget to take my medication. No, I do not miss my appointments… They will give me the appointment date, then I will go. If [I am] unable to go, [I'll] need to reschedule, [this] is very troublesome. I follow all [appointments]." (023, female, 78 years old) "I will mark down the [appointment] dates in my phone so that I won't forget. Hospital will also call or send letters to remind me of appointment dates…In the morning, I won't forget my medications. But at night, sometimes I may forget especially when I am having dinner outside." (031, male, 69 years old)	"Usually I didn't take my medicine when I am outside. The, maybe if I miss, I still take it but I take it late. I do go for all appointments." (050, male, 80 years old) "I do, I purposely skipped [medication] on Sunday…Because I told my doctor I want to detox myself…because medicine is a drug what, so you must detox. How you detox? So must skip on Sunday lah…check-up cannot skip, can postpone already… but skip 100% cannot [skip] lah. Die early…" (018, male, 78 years old)
Psychosocial coping			
Negative emotions related to the patient role (powerlessness and hopelessness)	X	"I don't want this [being chronically sick], I don't mind die [sic], I can go anytime I don't care one…" (033, female, 76 years old) "…We are just waiting for death…just a lifespan extension of a f ew years…" (011, male, 65 years old)	NA

Table 5. Themes and subthemes explaining readmission in the qualitative study (Cont'd)

Theme	Shared theme[a]	Illustrative quotes from readmitted patients	Illustrative quotes from non-readmitted patients
Care delivery			
Feeling like a burden and "left out" of care and participation in treatment decisions	X	"We realised the nurse just ignore her completely even when she is in pain so we asked 'why?' [The hospital staff then told us] 'we already gave her the laxative… we already do what we can'." (009, female, 79 years old) "Attentiveness of the nurses is not that great. I feel quite neglected." (039, female, 59 years old)	NA
Trust			
Wrong medicine or ineffective treatment was administered	X	"But sometimes the medications that the doctors give also no effect. [They work] very slow, [and the doctors] not say don't have effect [sic]. That's why I feel frustrated sometimes." (019, female, 54 years old) "I carry the inhaler with me as a "rescue" medication. I used the red one every morning and night, it's to protect the lungs, but it does not have much effect I feel. I just follow the doctor's instructions. I did told [doctor] but he [doctor] just asked me to continue using…" (031, male, 69 years old)	NA
Knowledge			
Adequate discharge instructions given	✓	"So if there is a wound there, keep it dry and don't keep it wet. Then constantly clean with antibacterial soap. [health care workers say:] Don't stick [anything] on it, don't put pressure on it, don't carry heavy things." (021, male, 40 years old) "In order to prevent lymphedema, I need to do massage on myself, they teach me how to do massage and then prevent myself from having cuts and all the infections…" (025, female, 39 years old)	"They told me not to touch it, because it can bleed, don't touch it, because [if I follow this] it will heal faster. They will just clean it up. So they […] just told me what to eat, [and] not to eat the oily food." (008, female, 50 years old) "They told me I can bathe but I need to dry it and be gentle to the wound..." (034, female, 65 years old)
Described having less knowledge and/or compliance to healthy diet	X	"I eat at outside. One day three meals at outside…Eat at outside is not good." (029, male, 76 years old) "…I would say 60–70% of my meals are from outside. Because I also work, so it is a bit difficult to eat at home. Try to [order healthy food]. Sometimes outside food a bit unavoidable…" (021, male, 40 years old)	NA

[a] In the shared themes column, ✓ denotes that these were indeed shared across the readmitted and non-readmitted patients, as illustrated by all quotes; X indicates that they were not; NA signifies therefore that the quote is not applicable

disease and a feeling of powerlessness and ineffective treatment, which again characterises the vulnerable chronic disease cohort. In addition, frequent readmission may lead to feelings of being ignored by hospital staff and family, lack of positive experience in hospital, and being excluded from the management decisions.

Readmission analysis models have been largely used for 2 distinct purposes. Government and authorities often use a risk-standardised readmission rates for comparing hospitals, reporting and reimbursement.[23] A further use of readmission model is to identify high-risk patients where intervention may reduce the risk. To be effective, the latter models should include variables that are easily available and have discriminatory power to differentiate different risk groups. Since interventions to reduce readmissions take time to implement, ideally such variables should be available in the early stage of index admission.[23,24] In the current study, many variables in our model are easily obtained from the demographic profiles, comorbidities and past histories. This is in contrast with previous studies that used variables recorded only on the discharge day.[25] All adult patients, including those admitted under the surgical disciplines, were covered in our study whereas previous literature included mainly medical patients.[6,7] Documentation of patient's perspective by qualitative data is uncommon in previous database analysis. Our patients' views elicited unique features in readmitted patients; this information should interest clinicians, administrators and policymakers.

Several limitations of the study are worth mentioning. Firstly, the current study comprises data collected within a single academic centre and thus need to be validated in other institutions. We could not collect data from other hospitals, which may potentially dilute the true hospital readmission rate if patients were readmitted to another hospital. Such extensive administrative data need extended period of data curation; therefore, we could not include more recent data. Finding actionable variables in the model was not the aim of the study as the interventions leading to improvement in readmission rates are generally multistep and complex. A meta-analysis found that interventions with at least 5 components, involving more individuals in care delivery (at least 2), and supporting patient capacity for self-care were more effective.[26] Larger social and environmental factors like status of primary care, ease of access to healthcare and functional status of the patient at discharge may also contribute to the readmission. Hospital and health system-related factors are mostly not captured in the current models, despite their influence on readmissions. These may include availability of hospital bed,[27] early follow-up,[28] effective medicine reconciliation[29] and inpatient quality of care.[30] Such data may not be easily available and although could improve the predictive power of the model, including them in the risk-standardisation model removes the very deficits that hospitals strive to improve by quality initiatives.[11]

CONCLUSION

Unplanned readmission is often seen as a separate singular event. It is, however, complex, and our study identified several factors related to patient (e.g. diagnosis, age, sex, ethnicity, comorbidity, subvention, visit to emergency department), procedure/medical (e.g. number of surgeries, number of discharge medications), and hospital (e.g. LOS, bill size) to be associated. Qualitative data elicited the vulnerability of readmitted patients, their negative emotions, and feeling of uselessness to the family and society at large. Understanding that discharged patients may remain in vulnerable health conditions, both physically and psychologically even after their hospital stay—a phenomenon termed "post-hospital syndrome"—is an important aspect of the changed healthcare scenario. Unless sufficient support is given to these patients, inability to cope with the burden of discharge may lead to readmissions.[26] Potential areas were identified for improvement, such as non-adherence to medical advice, involving patients in their care, and imparting knowledge about their disease condition and treatment.

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REFERENCES

1. Hasan O, Meltzer DO, Shaykevich SA, et al. Hospital readmission in general medicine patients: A prediction model. J Gen Intern Med 2010;25:211-9.
2. Yam CH, Wong EL, Chan FW, et al. Avoidable readmission in Hong Kong--system, clinician, patient or social factor? BMC Health Serv Res 2010;10:311.
3. Blunt I, Bardsley M, Grove A, et al. Classifying emergency 30-day readmissions in England using routine hospital data 2004–2010: What is the scope for reduction? Emerg Med J 2015;32:44-50.

4. Campione JR, Smith SA, Mardon RE. Hospital-level factors related to 30-day readmission rates. Am J Med Qual 2017;32:48-57.
5. Low LL, Liu N, Ong MEH, et al. Performance of the LACE index to identify elderly patients at high risk for hospital readmission in Singapore. Medicine (Baltimore) 2017;96:e6728.
6. Low LL, Lee KH, Hock Ong ME, et al. Predicting 30-day readmissions: Performance of the LACE index compared with a regression model among general medicine patients in Singapore. Biomed Res Int 2015;2015:169870.
7. Tan SY, Low LL, Yang Y, et al. Applicability of a previously validated readmission predictive index in medical patients in Singapore: A retrospective study. BMC Health Serv Res 2013; 13:366.
8. Wee S, Low S, Rao K, et al. Factors associated with hospital readmission and emergency visits among older adults–5-year experience in a busy acute hospital. J Clin Gerontol 2018;9:126-36.
9. van Walraven C, Dhalla IA, Bell C, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. CMAJ 2010;182:551-7.
10. Donzé J, Aujesky D, Williams D, et al. Potentially avoidable 30-day hospital readmissions in medical patients: Derivation and validation of a prediction model. JAMA Intern Med 2013; 173:632-8.
11. Kansagara D, Englander H, Salanitro A, et al. Risk prediction models for hospital readmission: A systematic review. JAMA 2011;306:1688-98.
12. Rubin DJ, Donnell-Jackson K, Jhingan R, et al. Early readmission among patients with diabetes: A qualitative assessment of contributing factors. J Diabetes Complications 2014;28:869-73.
13. Hodges P. Factors impacting readmissions of older patients with heart failure. Crit Care Nurs Q 2009;32:33-43.
14. Leventhal MJE, Riegel B, Carlson B, et al. Negotiating compliance in heart failure: Remaining issues and questions. Eur J of Cardiovas Nurs 2005;4:298-307.
15. Dilworth S, Higgins I, Parker V. Feeling let down: An exploratory study of the experiences of older people who were readmitted to hospital following a recent discharge. Contemp Nurse 2012; 42:280-8.
16. Creswell JW, Creswell JD. Research design: Qualitative, quantitative, and mixed methods approaches. SAGE Publications; 2014.
17. Sciences NOoBaS. Best practices for mixed methods research in the health sciences, 2018. (2nd ed.) U.S. Department of Health and Human Services, National Institutes of Health.
18. Peduzzi P, Concato J, Feinstein AR, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48:1503-10.
19. Tong A, Craig J, Sainsbury P. Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19:349-57.
20. King N, Horrocks C. Interviews in qualitative research. Los Angeles: SAGE; 2010.
21. Ritchie J, Lewis J, Nicholls C, et al. Qualitative research practice: A guide for social science students and researchers. London: SAGE; 2013.
22. Guest G, MacQueen KM, Namey EE. Applied thematic analysis. SAGE; 2012.
23. Coleman EA, Parry C, Chalmers S, et al. The care transitions intervention: Results of a randomized controlled trial. Arch Intern Med 2006;166:1822-8.
24. Jack BW, Chetty VK, Anthony D, et al. A reengineered hospital discharge program to decrease rehospitalization: A randomized trial. Ann Intern Med 2009;150:178-87.
25. Donzé J, Lipsitz S, Bates DW, et al. Causes and patterns of readmissions in patients with common comorbidities: Retrospective cohort study. BMJ 2013;347:f7171.
26. Leppin AL, Gionfriddo MR, Kessler M, et al. Preventing 30-day hospital readmissions: A systematic review and meta-analysis of randomized trials. JAMA Intern Med 2014;174:1095-107.
27. Fisher E, Goodman D, Skinner J, et al. Health care spending, quality, and outcomes: More isn't always better. 2009.
28. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among medicare beneficiaries hospitalized for heart failure. JAMA 2010;303:1716-22.
29. Kripalani S, Jackson AT, Schnipper JL, et al. Promoting effective transitions of care at hospital discharge: A review of key issues for hospitalists. J Hosp Med 2007;2:314-23.
30. Weissman JS, Ayanian JZ, Chasan-Taber S, et al. Hospital readmissions and quality of care. Med Care 1999:490-501.

ORIGINAL ARTICLE

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Immunomodulator use in paediatric severe sepsis and septic shock

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ABSTRACT

Introduction: The use of drugs that modulate the immune system during paediatric severe sepsis and septic shock may alter the course of disease and is poorly studied. This study aims to characterise these children who received immunomodulators and describe their clinical outcomes.

Methods: This is a retrospective chart review of patients with severe sepsis and septic shock admitted into the paediatric intensive care unit (PICU). Clinical, haematological and outcome characteristics of patients with or without exposure to immune-modulating drugs were compared. Primary outcome was PICU mortality; secondary outcomes were 28-day ventilator-free days (VFD) and intensive care unit-free days (IFD). Univariate and multivariable analyses were performed for these outcomes.

Results: A total of 109 patients with paediatric severe sepsis or septic shock were identified. Of this number, 47 (43.1%), 16 (14.7%) and 3 (2.8%) patients received systemic corticosteroids, intravenous immunoglobulins and granulocyte colony stimulating factor, respectively. Patients who received immune-modulating drugs were more likely to require invasive ventilation (38/54 [70.4%] versus 26/55 [47.3%], *P*=0.019) compared to those who did not. PICU mortality was indifferent between the 2 groups (20/54 [37.0%] vs 11/55 [20.0%], *P*=0.058) even after accounting for chronic complex conditions and admission organ dysfunction (PELOD score) (adjusted odds ratio 1.90, confidence interval [0.72–5.01], *P*=0.193). However, VFD (19.5 [0–28] vs 25 [12–28] days, *P*=0.038) and IFD (15 [0–24] vs 22 [9–26] days, *P*=0.024) were decreased in the immunomodulator group compared to the non-immunomodulator group.

Conclusion: Immune-modulating drugs were frequently used in paediatric severe sepsis and septic shock. Patients who received these drugs seemed to require more PICU support. Further studies are required to examine this association thoroughly.

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Keywords: Children, immunomodulatory drugs, infection, paediatric intensive care unit, sepsis

INTRODUCTION

Paediatric sepsis is one of the main causes of childhood mortality.[1] Globally, paediatric severe sepsis and septic shock accounts for 6.2% to 23.1% of paediatric intensive care unit (PICU) admissions, and mortality rates can be as high as 21.3% in North America and Europe to 50.0% in Asia.[2-4] Of particular concern are the outcomes in the increasing number of children with significant comorbidities such as malignancy, or those with chronic organ impairment who survive into later years and pose new considerations to the management of severe sepsis and septic shock.[5-7]

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[8] This definition recognises the role of the host immune response to an infection. Sepsis is thought to be driven by an initial hyper-inflammatory response followed by an immunosuppressive phase. However, recent studies have shown a shift towards a new paradigm, where a prolonged inflammatory and anti-inflammatory state

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CLINICAL IMPACT

What is New

- Our report shows frequent exposure to immune-modulating drugs in children with severe sepsis and septic shock.
- The reactive increase in white cell indices expected during the course of sepsis is absent in children exposed to immune-modulating drugs.
- Exposure to immune-modulating drugs during paediatric severe sepsis and septic shock is associated with greater duration of invasive mechanical ventilation and paediatric intensive care stay.

Clinical Implications

- Exposure to immune-modulating drugs during paediatric severe sepsis and septic shock is associated with worsened clinical outcomes and warrants further study.

occurring simultaneously is driven by a dysfunctional innate and suppressed adaptive immunity, which together results in persistent organ injury and death.[9-11] Therefore, it has been theorised that immunotherapy holds promise in modulating the immune system. However, the use of immunotherapy in treating sepsis has been met with mixed results.[12,13] Recent clinical trials involving corticosteroids showed mixed results regarding mortality and hospitalisation.[14,15] A Cochrane review on intravenous immunoglobulin (IVIG) revealed mortality benefit in adults with sepsis but not in neonates.[16] Statistically proven mortality benefit has yet to be found with the use of granulocyte-colony stimulating factor (GCSF), interferon-gamma, interleukin-7 and anti-PD1 (programmed cell death protein 1) in sepsis.[17-20]

While several studies have been conducted in the paediatric setting, these have largely involved limited sample sizes with inconclusive results.[21-23] Nevertheless, we suspect these therapies are often utilised in the management of paediatric sepsis and septic shock.[24] In this study, we review cases of paediatric severe sepsis and septic shock in our institution to determine the characteristics of patients who concurrently received immune-modulating drugs, particularly corticosteroids, IVIG and GCSF, and examine their outcomes.

METHODS

This is a retrospective cohort study conducted in the PICU of KK Women's and Children's Hospital, a university-affiliated tertiary hospital in Singapore. This study was approved by the SingHealth Centralised Institutional Review Board (reference number: 2016/2171) and a waiver of consent was granted.

Patients were identified based on their discharge diagnosis from hospital-wide electronic medical databases. Patients aged 0 to 18 years admitted to the PICU between 1 January 2010 and 31 October 2017 were included upon meeting the diagnostic criteria for paediatric severe sepsis or septic shock as defined by the International Pediatric Sepsis Consensus Conference.[25] The use of corticosteroids, GCSF, IVIG, plasma exchange or other biologic drugs at the time of PICU admission for sepsis, regardless of indication, was considered to play a direct role on the immune system and categorised in the immunomodulator group. Patients who did not meet the above criteria were placed under the non-immunomodulator group.

Demographic, clinical, microbiological and detailed treatment data were obtained from electronic medical records. Significant chronic comorbidities were defined by the complex chronic conditions list of diseases.[26] Complex chronic conditions refer to a list of medical conditions that can be reasonably expected to last at least 12 months (unless death intervenes) and to involve either several organ systems or at least 1 organ system severely enough to require specialty paediatric care and probably some period of hospitalisation in a tertiary care centre.[26] Severity of illness scores, Pediatric Index of Mortality (PIM) 2 score and the Pediatric Logistic Organ Dysfunction (PELOD) score were obtained on PICU admission.[27-29] Organ dysfunction was defined based on the International Pediatric Sepsis Consensus Conference definition.[25] Day 1 of severe sepsis and/or septic shock was defined as the day the patient fulfilled the criteria for severe sepsis or septic shock in the PICU. 28-day ventilator-free days (VFD) is defined as days alive and free from invasive mechanical ventilation up to 28 days—this is to account for early deaths.[30] Similarly, 28-day intensive care unit-free days (IFD) is defined as days alive and discharged from the PICU up to 28 days.

Statistical analysis

We compared patients in 2 groups: the immunomodulation group and non-immunomodulation group. Clinical characteristics were compared between the 2 groups. Haematological markers across the first 7 days of sepsis including the total leukocyte, lymphocyte, neutrophil and platelet counts were also compared between the 2 groups. The primary outcome of this study was PICU mortality. Secondary outcomes included VFD and IFD. Categorical and continuous variables were expressed as counts (percentages) and median (interquartile range),

respectively. The Fisher's exact test and Wilcoxon rank sum test were used to compare categorical and continuous variables, respectively. Multivariable logistic regression for the primary outcome was performed with a priori determined covariates: presence of chronic complex conditions, organ dysfunction (summarised as the PELOD score) and the use of immunomodulators. Association from logistic regression was characterised as odds ratio (OR) with corresponding 95% confidence intervals (CI). The logistic regression was repeated, excluding patients exposed to immunomodulators for autoimmune or immune related indications, as a sensitivity analysis. Secondary outcomes were also analysed with respect to immunomodulator versus non-immunomodulator groups. Analysis was performed on STATA software version 15.1 (StataCorp, College Station, US). All tests were 2-tailed and P value <0.05 was accepted as statistically significant.

RESULTS

There were 109 patients who met the criteria for paediatric severe sepsis or septic shock (Table 1). Clinical characteristics were similar between the immunomodulator and non-immunomodulator groups in terms of age, presence of complex chronic conditions, PIM2, PELOD scores and source of sepsis on admission. The most common source of sepsis was pneumonia (59/109, 54.1%), followed by gastrointestinal (16/109, 14.7%) and musculoskeletal (8/109, 7.3%) (Table 2). Sepsis from a single aetiologic agent was most commonly bacterial (28/109, 25.7%), followed by viral (25/109, 22.9%). Co-infections were present in 19 (17.4%) patients and no identifiable aetiologic agent was found in 32 (29.4%).

Immunomodulating therapies, regardless of indications, were used in 54 (49.5%) patients. Systemic corticosteroid was the most common immunomodulator (47/109, 43.1%), followed by IVIG (16/109, 14.7%) and GCSF (3/109, 2.8%). One patient who fulfilled the criteria for severe sepsis also received therapeutic plasma exchange. There were no patients who concurrently received chemotherapy or biologics during the course of sepsis in the PICU. The clinical indications for use of these therapies are summarised in Table 3. The median total white cell count was lower in the group receiving immunomodulators throughout the first 7 days of study (except on day 2, which did not reach statistical significance) (Fig. 1A). The trend of total white cell count was also observed to increase across the 7 days in those without exposure to immunomodulators, but this was not seen in those on immunomodulator group. A similar trend was seen in the absolute neutrophil and lymphocyte counts, especially toward the end of the 7 days (Figs. 1B and 1C). There was no difference in the platelet count over the 7 days of sepsis between the 2 groups (Fig. 1D).

Despite having similar admission characteristics, patients in the immunomodulation group required greater PICU support compared to those in the non-immunomodulation group, including invasive ventilation (38/54, 70.4% vs 26/55, 47.3%; P=0.019) and inotropes (41/54, 75.9% vs 32/55, 58.2%; P=0.067), though this did not reach statistical significance. Ventilator- and ICU-free days were also reduced in the immunomodulator group (20 [0–28] vs 25 [12–28]; P=0.038 and 15 [0–24] vs 22 (9–26); P=0.024, respectively). In this sepsis cohort, a total of 31 deaths (28.4%) occurred. PICU mortality was higher among patients receiving immunomodulating therapy compared to patients who did not receive it (20/54 [37.0%] vs 11/55 [20.0%]; P=0.058), although this was not statistically significant (Table 1). Significantly greater number of patients with malignancy received immunomodulator therapy as compared to those who did not (14/54 [25.9%] vs 3/55 [5.5%]; P=0.004). After accounting for complex chronic conditions and admission organ dysfunction (PELOD score), exposure to immunomodulator therapy was not associated with an increase in PICU mortality (adjusted odds ratio 1.90 (95% confidence interval 0.72–5.01); P=0.193) (Table 4). In the sensitivity analysis excluding patients exposed to immunomodulators for autoimmune or immune related indications, the results were similar.

DISCUSSION

Our report shows frequent exposure to immunomodulating drugs in children with severe sepsis and septic shock. This group of children seem to require greater PICU support including mechanical ventilation and inotropes. After adjusting for complex chronic conditions and admission organ dysfunction, immunomodulators were associated with an almost 2-fold increased mortality, though this did not achieve statistical significance due to the small cohort size. A reactive and expected increase in white cell indices was observed in children with severe sepsis and septic shock. However, this was absent in those receiving immunomodulators.

The use of immunomodulators may inherently bias towards a group of patients with underlying immunological defects (e.g. malignancies, chemotherapy and autoimmune disease), though in the logistic regression model, these conditions were accounted for. In our cohort, 17 patients had malignancy and 3 patients had haematological disease, for which 14 patients and

Table 1. Characteristics of patients who received immune modulating therapy

	Immune modulation (n=54)	No immune modulation (n=55)	All (N=109)	*P* value
Age, median (IQR), years	9.3 (1.4–13.0)	9.4 (0.4–13.1)	9.4 (2.4–13.0)	0.952
Male sex, no. (%)	22 (40.7)	29 (52.7)	51 (46.8)	0.251
Weight, median (IQR), kg	24.7 (12.7–37.8)	24.4 (11.2–40.0)	24.4 (11.5–40.0)	0.971
CCC, no. (%)	31 (57.4)	23 (41.8)	54 (49.5)	0.127
Malignancy	14 (25.9)	3 (5.5)	17 (15.6)	**0.004**
Haematology-Immunology	2 (3.7)	1 (1.8)	3 (2.8)	0.618
PIM 2, median (IQR)	3.3 (1.3–7.1)	3.5 (1.2–9.6)	3.4 (1.3–8.9)	0.854
PELOD, median (IQR)	13 (11–22)	11 (10–21)	12 (10–21)	0.123
Source of sepsis, no. (%)				0.603
Pneumonia	26 (48.2)	31 (56.4)	57 (52.3)	
Central nervous system	4 (7.4)	3 (5.5)	7 (6.4)	
Musculoskeletal	6 (11.1)	2 (3.6)	8 (7.3)	
Gastrointestinal	7 (13.0)	10 (18.1)	17 (15.6)	
Blood stream	4 (7.4)	2 (3.6)	6 (5.5)	
Others	7 (13.0)	7 (12.7)	14 (12.8)	
Bacteraemia, no. (%)	12 (22.6)	11 (19.6)	23 (21.2)	0.815
Source control, no. (%)	4 (7.4)	7 (12.7)	11 (10.1)	0.527
Inotropes, no. (%)	41 (75.9)	32 (58.2)	73 (67.0)	0.067
Non-invasive ventilation, no. (%)	13 (24.1)	18 (32.7)	31 28.4)	0.397
Invasive ventilation, no. (%)	38 (70.4)	26 (47.3)	64 (58.7)	**0.019**
Duration of invasive ventilation, no. (%), days	3 (0, 6)	0 (0, 4)	2 (0, 5)	0.134
VFD, median (IQR), days	19.5 (0–28)	25 (12–28)	23 (0–28)	**0.038**
Multiorgan dysfunction, no. (%)	51 (94.4)	46 (83.6)	97 (89.0)	0.124
ECMO, no. (%)	6 (11.1)	3 (5.5)	9 (8.3)	0.320
Mortality, no. (%)	20 (37.0)	11 (20.0)	31 (28.4)	0.058
ICU LOS, median (IQR), days	5 (2–11)	3 (1–7)	4 (2–9)	0.076
IFD, median (IQR), days	15 (0–24)	22 (9–26)	21 (0–25)	**0.024**
Hospital LOS, median (IQR), days	15 (7–29)	10 (5–19)	12 (6–22)	0.146

CCC: complex chronic conditions; ECMO: extra-corporeal membrane oxygenation; ICU: intensive care unit; IFD: 28-day intensive care unit-free days; IQR: interquartile range; LOS: length of stay; PELOD: Pediatric Logistic Organ Dysfunction; PIM: Pediatric Index of Mortality; VFD: 28-day ventilator-free days

Categorical variables are reported as count (percentages) and continuous variables are reported as median (IQR)

P values in bold are significant

2 patients, respectively received immunomodulator therapy. In the same way, patients with significant organ dysfunction at PICU admission who were likely to bias the outcome negatively were also accounted for. Nevertheless, our study seems to suggest that immunomodulator therapy was associated with an almost 2-fold increase in mortality, although this was statistically not significant. A prospective study with a larger sample size would provide a clearer association and determination of statistical significance.

Table 2. Aetiologic agents involved in paediatric severe sepsis and septic shock

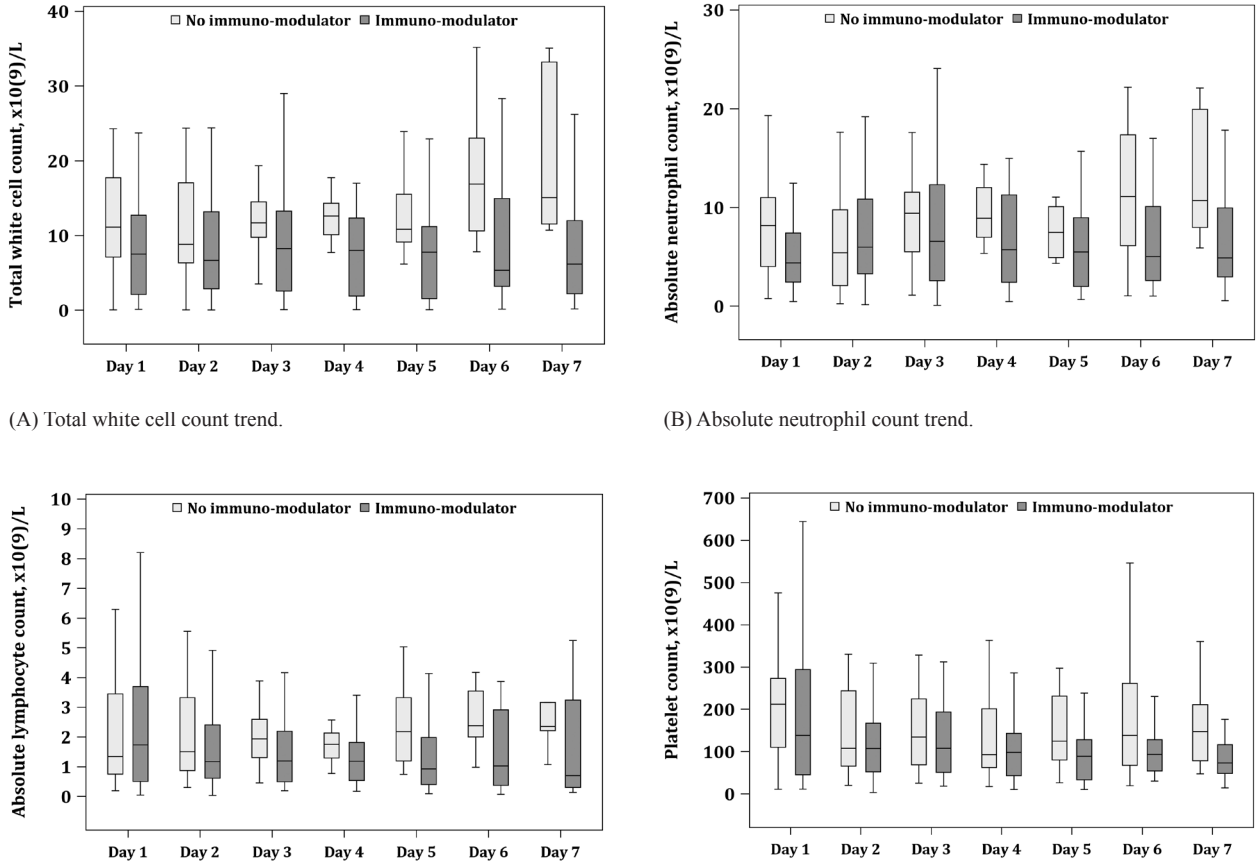
Source of sepsis	None (n=32)	Single aetiologic agent			Co-infection			
		Bacteria (n=28)	Virus (n=25)	Fungi (n=5)	Bacteria and virus (n=9)	Bacterial and fungi (n=3)	Virus and fungi (n=6)	Bacteria, virus and fungi (n=1)
Pneumonia	15	13	16	3	4	1	6	1
Genito-urinary	0	1	0	0	1	0	0	0
Central nervous system	0	2	4	0	1	0	0	0
Musculoskeletal	4	4	0	0	0	0	0	0
Gastrointestinal	5	2	3	1	3	2	0	0
Blood stream	0	6	0	0	0	0	0	0
Others	2	0	2	1	0	0	0	0
No primary source	6	0	0	0	0	0	0	0

Table 3. Indications for immune-modulating therapy

Immune modulating therapy	Indication	Patients, no.
Systemic corticosteroids (n=47)	Septic shock	26
	Respiratory disease Pulmonary hemosiderosis Pulmonary fibrosis Asthma ARDS Airway oedema	11
	Premedication for blood transfusion (or other drugs)	5
	Others Takayasu arteritis Hypoglycaemia Acute necrotising encephalomyelitis Autoimmune haemolysis Resistant mycoplasma infection	5
IVIG (n=16)	Infection Severe sepsis Influenza encephalitis Toxic shock syndrome Myocarditis Adenovirus infection	10
	Immunoglobulin replacement Post HSCT Primary immunodeficiency Haemophagocytic histiocytosis	3
	Autoimmune disease Takayasu arteritis Kawasaki disease Autoimmune haemolysis	3
GSCF (n=3)	Severe neutropenic sepsis Post-chemotherapy Haemophagocytic histiocytosis	3
Therapeutic plasma exchange (n=1)	Autoimmune haemolysis	1

ARDS: acute respiratory distress syndrome; GCSF: granulocyte-colony stimulating factor; HSCT: haematopoietic stem cell transplant; IVIG: intravenous immunoglobulin

Fig. 1. Trend of haematological markers across first 7 days of sepsis in patients with and without immunomodulator therapy.



(A) Total white cell count trend.

(B) Absolute neutrophil count trend.

(C) Absolute leukocyte count trend.

(D) Platelet count trend.

Table 4. Multivariable logistic regression for paediatric intensive care unit mortality

Covariate	Univariate			Multivariable		
	OR	95% CI	*P* value	OR	95% CI	*P* value
CCC	2.86	1.19–6.88	0.019	2.16	0.80–5.82	0.127
PELOD	1.11	1.05–1.16	<0.001	1.10	1.05–1.16	<0.001
Immuno-modulation	2.35	0.99–5.57	0.051	1.90	0.72–5.01	0.193

Replacing "CCC" with "malignancy" generated similar results
CCC: complex chronic conditions; CI: confidence interval; OR: odds ratio; PELOD: Pediatric Logistic Organ Dysfunction

The majority of immunomodulator use consisted of systemic corticosteroids (47/54, 87.0%). Though indications for the use of corticosteroids, in our cohort, were largely adrenal suppression and respiratory, corticosteroids have myriad effects on other systems and have been associated with hyperglycemia, impaired wound healing, hospital acquired infections, as well as increased organ failure and mortality.[31,32] In addition, corticosteroids also contribute to the development of myopathy[33,34] and can prolong the duration of invasive ventilation and hospitalisation.[35] These negative effects may have contributed as a cause for the increased mortality, and decreased VFD and IFD observed in our cohort, however, due to the retrospective design, only an association can be made. The Stress Hydrocortisone in Pediatric Septic Shock (SHIPSS) trial specifically seeks to determine if adjunctive hydrocortisone will significantly reduce the proportion of children with

septic shock from death or subsequent poor quality of life (clinicaltrial.gov NCT03401398). The outcome of this randomised controlled, double-blinded study is anticipated to provide a definitive answer to the current gap in knowledge on the effect of corticosteroids in sepsis.

Mortality benefit was found in adult patients with sepsis who were treated with IVIG.[36] These effects may be attributed to IVIG's role in immunoglobulin replacement and its potential effects on B cells, T cells, antibodies, complement pathways and cytokines in adult neuromuscular disorders and immune neuropathies.[37] However, a meta-analysis evaluating the effects of IVIG in neonatal infections found no mortality benefit.[38] Our paediatric cohort may not be directly comparable to either the adult nor neonatal population; however, our data suggest a tendency to poorer outcomes in patients who receive drugs that have an immunomodulating effect including IVIG. A reduction in the overall white cell count has also been described in patients from other studies receiving IVIG consistent with a reduction in both absolute neutrophil count and absolute lymphocyte count (ALC); however the mechanism was described as multifactorial[39,40] and not fully understood.[22] The reduction in ALC may also be contributed by the suppressive effects of corticosteroids on ALC.[41,42] The overall reduction of white cell differentials may also be a reflection of the biphasic sepsis response, whereby patients who survive the initial hyper-inflammatory phase enter a protracted hypo-inflammatory phase characterised by persistent inflammation and immune suppression.[43,44] Immune cell depletion in this phase is driven by caspase-mediated apoptosis.[45] Compromise in innate defences[46,47] and T cell exhaustion[48] contribute to a state of malfunctional immune tolerance and susceptibility to further infections and mortality.[44]

There are several limitations in this study's findings. Firstly, due to the small sample size, we could not establish an association between mortality and immunomodulation therapy despite an almost 2-fold increase in mortality, nor perform additional subanalysis (e.g. to examine each immune-modulator therapy separately). The current sample size of 109 achieves only 66% power to detect a difference in mortality of 20% between the 2 groups, using the two-sided Fisher's exact test and assuming a significance level as 5%. A prospective study design with a larger cohort (n=182) is recommended to address these limitations and adequately power the study (β=80%) to detect a mortality difference.

We also were unable to determine causation between the use of immunomodulation and worsened primary and secondary outcomes given the retrospective nature of this study. Indications for these immunomodulation therapies were also heterogenous and physician dependent. Lastly, other important variables such as malnutrition that may have affected the immune system were not accounted for.

CONCLUSION

Exposure to immune-modulating drugs during paediatric severe sepsis and septic shock is associated with higher use of invasive ventilation and less IFD and VFD. A reactive and expected increase in white cell indices was observed during the course of sepsis; however, this was absent in children receiving immunomodulators. A prospective study is recommended to further determine the effectiveness of immune-modulating therapy on primary and secondary outcomes in severe sepsis and septic shock in the paediatric population.

Disclosures

There are no affiliations or financial involvement with any commercial organisations in this study. An abstract of the current work has been presented at the 6th SG-ANZICS Asia Pacific Intensive Care Forum 2019.

REFERENCES

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395:200-11.
2. Tan B, Wong JJ, Sultana R, et al. Global Case-Fatality Rates in Pediatric Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis. JAMA Pediatr 2019;173:352-62.
3. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, et al. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med. 2018;6:223-30.
4. Wong JJ, Ho SX, Lee AOC, et al. Positive Fluid Balance is Associated with Poor Clinical Outcomes in Paediatric Severe Sepsis and Septic Shock. Ann Acad Med Singap 2019;48:290-7.
5. Esper AM, Moss M, Lewis CA, et al. The role of infection and comorbidity: Factors that influence disparities in sepsis. Crit Care Med 2006;34:2576-82.
6. Adamson PC. Improving the outcome for children with cancer: Development of targeted new agents. CA Cancer J Clin 2015;65: 212-20.
7. Boneva RS, Botto LD, Moore CA, et al. Mortality associated with congenital heart defects in the United States: trends and racial disparities, 1979-1997. Circulation 2001;103:2376-81.
8. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
9. Boomer JS, To K, Chang KC, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA 2011;306: 2594-605.

10. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. Nat Rev Immunol 2008;8:776-87.
11. Xiao W, Mindrinos MN, Seok J, et al. A genomic storm in critically injured humans. J Exp Med 2011;208:2581-90.
12. Lo AH, Kee AC, Li A, et al. Controversies in Sepsis Management-What is the Way Forward? Ann Acad Med Singap 2020;49:661-8.
13. Chong SL, Ong GY, Venkataraman A, et al. The golden hours in paediatric septic shock--current updates and recommendations. Ann Acad Med Singap 2014;43:267-74.
14. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. N Engl J Med 2018;378:809-18.
15. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N Engl J Med 2018; 378:797-808.
16. Alejandria MM, Lansang MA, Dans LF, et al. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. Cochrane Database Syst Rev 2013:CD001090.
17. Vignon P, Laterre PF, Daix T, et al. New Agents in Development for Sepsis: Any Reason for Hope? Drugs 2020;80:1751-61.
18. Payen D, Faivre V, Miatello J, et al. Multicentric experience with interferon gamma therapy in sepsis induced immunosuppression. A case series. BMC Infect Dis 2019;19:931.
19. Francois B, Jeannet R, Daix T, et al. Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. JCI Insight 2018;3:e98960.
20. Bo L, Wang F, Zhu J, et al. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) for sepsis: a meta-analysis. Crit Care 2011;15:R58.
21. Carr R, Modi N, Dore C. G-CSF and GM-CSF for treating or preventing neonatal infections. Cochrane Database Syst Rev 2003;2003:CD003066.
22. Wong PH, White KM. Impact of Immunoglobulin Therapy in Pediatric Disease: a Review of Immune Mechanisms. Clin Rev Allergy Immunol 2016;51:303-14.
23. Zimmerman JJ, Williams MD. Adjunctive corticosteroid therapy in pediatric severe sepsis: observations from the RESOLVE study. Pediatr Crit Care Med 2011;12:2-8.
24. Mathias B, Mira JC, Larson SD. Pediatric sepsis. Curr Opin Pediatr 2016;28:380-7.
25. Goldstein B, Giroir B, Randolph A, et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2-8.
26. Edwards JD, Houtrow AJ, Vasilevskis EE, et al. Chronic conditions among children admitted to U.S. pediatric intensive care units: their prevalence and impact on risk for mortality and prolonged length of stay. Crit Care Med 2012;40:2196-203.
27. Leteurtre S, Duhamel A, Grandbastien B, et al. Paediatric logistic organ dysfunction (PELOD) score. Lancet 2006;367:897.
28. Wong JJ, Hornik CP, Mok YH, et al. Performance of the Paediatric Index of Mortality 3 and Paediatric Logistic Organ Dysfunction 2 Scores in Critically Ill Children. Ann Acad Med Singap 2018; 47:285-90.
29. Slater A, Shann F, Pearson G. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 2003;29:278-85.
30. Yehya N, Harhay MO, Curley MAQ, et al. Reappraisal of Ventilator-Free Days in Critical Care Research. Am J Respir Crit Care Med 2019;200:828-36.
31. Schacke H, Docke WD, Asadullah K. Mechanisms involved in the side effects of glucocorticoids. Pharmacol Ther 2002;96:23-43.
32. Yung M, Wilkins B, Norton L, et al. Glucose control, organ failure, and mortality in pediatric intensive care. Pediatr Crit Care Med 2008;9:147-52.
33. Bercker S, Weber-Carstens S, Deja M, et al. Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. Crit Care Med 2005;33:711-5.
34. Lacomis D, Giuliani MJ, Van Cott A, et al. Acute myopathy of intensive care: clinical, electromyographic, and pathological aspects. Ann Neurol 1996;40:645-54.
35. Amaya-Villar R, Garnacho-Montero J, Garcia-Garmendia JL, et al. Steroid-induced myopathy in patients intubated due to exacerbation of chronic obstructive pulmonary disease. Intensive Care Med 2005;31:157-61.
36. Yang Y, Yu X, Zhang F, et al. Evaluation of the Effect of Intravenous Immunoglobulin Dosing on Mortality in Patients with Sepsis: A Network Meta-analysis. Clin Ther 2019;41:1823-38.e4.
37. Hartung HP. Advances in the understanding of the mechanism of action of IVIg. J Neurol 2008;255(Suppl 3):3-6.
38. Alomran A. Intravenous Immunoglobulin Doesn't Decrease Mortality for Suspected or Proven Sepsis in the Neonate. J Clin Neonatol 2013;2:163-5.
39. Cicha A, Fischer MB, Wesinger A, et al. Effect of intravenous immunoglobulin administration on erythrocyte and leucocyte parameters. J Eur Acad Dermatol Venereol 2018;32:1004-10.
40. Koffman BM, Dalakas MC. Effect of high-dose intravenous immunoglobulin on serum chemistry, hematology, and lymphocyte subpopulations: assessments based on controlled treatment trials in patients with neurological diseases. Muscle Nerve 1997;20:1102-7.
41. Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann Intern Med 1976;84:304-15.
42. Heming N, Sivanandamoorthy S, Meng P, et al. Immune Effects of Corticosteroids in Sepsis. Front Immunol 2018;9:1736.
43. Nedeva C, Menassa J, Puthalakath H. Sepsis: Inflammation Is a Necessary Evil. Front Cell Dev Biol 2019;7:108.
44. Hotchkiss RS, Monneret G, Payen D. Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol 2013;13:862-74.
45. Hotchkiss RS, Osmon SB, Chang KC, et al. Accelerated lymphocyte death in sepsis occurs by both the death receptor and mitochondrial pathways. J Immunol 2005;174:5110-8.
46. Huang X, Venet F, Wang YL, et al. PD-1 expression by macrophages plays a pathologic role in altering microbial clearance and the innate inflammatory response to sepsis. Proc Natl Acad Sci USA 2009;106:6303-8.
47. Forel JM, Chiche L, Thomas G, et al. Phenotype and functions of natural killer cells in critically-ill septic patients. PLoS One 2012;7:e50446.
48. Condotta SA, Khan SH, Rai D, et al. Polymicrobial Sepsis Increases Susceptibility to Chronic Viral Infection and Exacerbates CD8+ T Cell Exhaustion. J Immunol 2015;195:116-25.

REVIEW ARTICLE

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Does pulmonary metastasectomy of colorectal metastases translate to better survival? A systematic review

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ABSTRACT

Introduction: Surgical resection of the primary and metastatic tumour is increasingly recommended in suitable patients with metastatic colorectal cancer (CRC). While the role of metastasectomy is well studied and established in colorectal liver metastasis, evidence remains limited in pulmonary metastases. This systematic review was conducted to examine the current evidence on the role of lung metastasectomy (LUM) in CRC.

Methods: Three databases were systematically searched, to identify studies that compared survival outcomes of LUM, and factors that affected decision for LUM.

Results: From a total of 5,477 records, 6 studies were eventually identified. Two papers reported findings from one randomised controlled trial and 4 were retrospective reviews. There was no clear survival benefit in patients who underwent LUM compared to those who did not. When compared against patients who underwent liver metastasectomy, there was also no clear survival benefit. Patients who underwent LUM were also more likely to have a single pulmonary tumour, and metachronous disease.

Conclusion: The evidence suggests a role for LUM, but is limited by inherent selection bias in retrospective reviews, and the single randomised clinical trial performed was not completed. More prospective studies are required to understand the true effect of LUM on outcomes in metastatic CRC.

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Keywords: Colorectal cancer, pulmonary metastasectomy, pulmonary metastases, survival

INTRODUCTION

Colorectal cancer (CRC) is the one of most common cancers worldwide. Metastatic disease occurs in approximately half of all CRC patients, in either synchronous or metachronous presentations.[1] These patients form a heterogenous group that vary in presentation, disease progression and treatment options.

Advancements in surgery and chemotherapy have revolutionised the management of metastatic CRC. In addition to chemotherapy, surgical clearance of all disease, whether primary or metastatic, is often recommended in suitable patients. Reported 5-year survival after R0 resection of primary and metastatic tumours in metastatic CRC ranges from 40.0 to 58.0%, compared to just 3.0 to 5.0% without any treatment.[2-5]

While the role of liver metastasectomy or utilisation of other adjuncts to address colorectal liver metastases has increasingly been advocated, many are now debating if such a similar approach can be advocated in patients with lung metastases from CRC. Although slightly less common, pulmonary metastases (PM) still occur in 10.0–20.0% of patients with CRC, with approximately half of these patients presenting with synchronous metastases.[6,7] Patients with PM are now being considered for curative metastasectomy if both the primary CRC and PM can be resected with clear margins and if they are fit.[6] In spite of the burgeoning literature looking at liver metastasectomy (LIM), limited evidence for lung metastasectomy (LUM) exists with a majority of them being case series and retrospective studies that

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CLINICAL IMPACT

What is New

- There was no clear survival benefit in patients who underwent lung metastasectomy (LUM) compared to those who did not.
- Evidence suggests a role for LUM, but is limited by inherent selection bias.

Clinical Implications

- Role of metastasectomy remains limited in pulmonary metastases.
- More prospective studies are required to understand the true effect of LUM on outcomes in metastatic colorectal cancer.

reported acceptable survival rates.[6,8] However, there are currently no guidelines on the role of resection of pulmonary metastases from CRC. This review aims to examine the current literature and evidence on the role of pulmonary metastasectomy in colorectal cancer.

METHODS

Search strategy and selection criteria

A systematic search of three databases (PubMed, Embase, and CENTRAL) was conducted on 5 June 2020. The search strategy aimed to capture terms that were relevant to pulmonary metastases, LUM and colorectal cancer. The search strategy was kept deliberately broad to mitigate the possibility of relevant articles being missed out.

> Terms searched were: ("pulmonary metastasectomy" OR "lung metastasectomy" OR "surgery" OR "resection") AND ("pulmonary metastases" OR "pulmonary metastasis" OR "lung metastases" OR "lung metastasis") AND ("colorectal cancer" OR "colon cancer" OR "colorectal").

We included all studies that reported survival as a primary outcome of surgical resection of a colorectal pulmonary metastasis that were published in English. Studies were excluded if they (1) did not collect primary data (e.g. reviews, meta-analyses or commentaries), (2) did not include any comparators (i.e. case series), (3) enrolled patients with a non-colorectal primary cancer site, (4) did not involve any form of surgical treatment, and (5) focused specifically on reporting surgical techniques. We also excluded studies that (6) only enrolled specific subgroups of the patient population of interest (e.g. only repeat LIM or LUM, or simultaneous liver and lung metastases) due to the potential for these subgroup disease and treatment characteristics to confound the overall impact of LUM.

Study selection, data extraction, and analysis

The search strategy was applied to each of the 3 databases and 1 co-author (BES) compiled the resultant records using EndNote X8. These were subjected to a preliminary screening of titles and abstracts by 4 co-authors (BES, YKC, LYX and YXL) using the study selection criteria detailed above. The full texts of these shortlisted records were then reviewed by 4 co-authors (JL, BES, YKC and YXL). To mitigate possible selection biases, 10% of each co-author's assigned full texts were independently reviewed by another co-author, and any disagreements were resolved via consensus among all authors.

Quality assessment and risk of bias were performed for each included study by two co-authors (BES and JL) using the appropriate Joanna Briggs Institute (JBI) critical appraisal tools checklist (based on the study design).[9] Data extraction for the finalised sample of studies included was performed by 1 co-author (BES) using a standardised electronic data collection form. We then descriptively summarised study and sample characteristics, key findings and limitations from each of the included studies.

RESULTS

The search yielded a total of 5,477 records (1,472 from PubMed, 3,926 from Embase and 79 from CENTRAL), of which 1,232 duplicates were removed. Of the remaining 4,245 records, 4,049 were excluded after preliminary screening of titles and abstracts based on our study selection criteria. The remaining 196 records were subjected to a full text review, resulting in a final sample of 6 articles. The PRISMA flow chart illustrating the search and study selection process can be found in Fig. 1. These 6 studies satisfied more than 50% of the JBI critical appraisal criteria, and were deemed to be of acceptable quality. The studies are summarised in Table 1, describing the year of publication, country of origin, sample size, study design, disease-free survival (DFS), overall survival (OS), interval to LUM from diagnosis, number of lung metastases, concurrent liver and lung metastases, and chemotherapy.

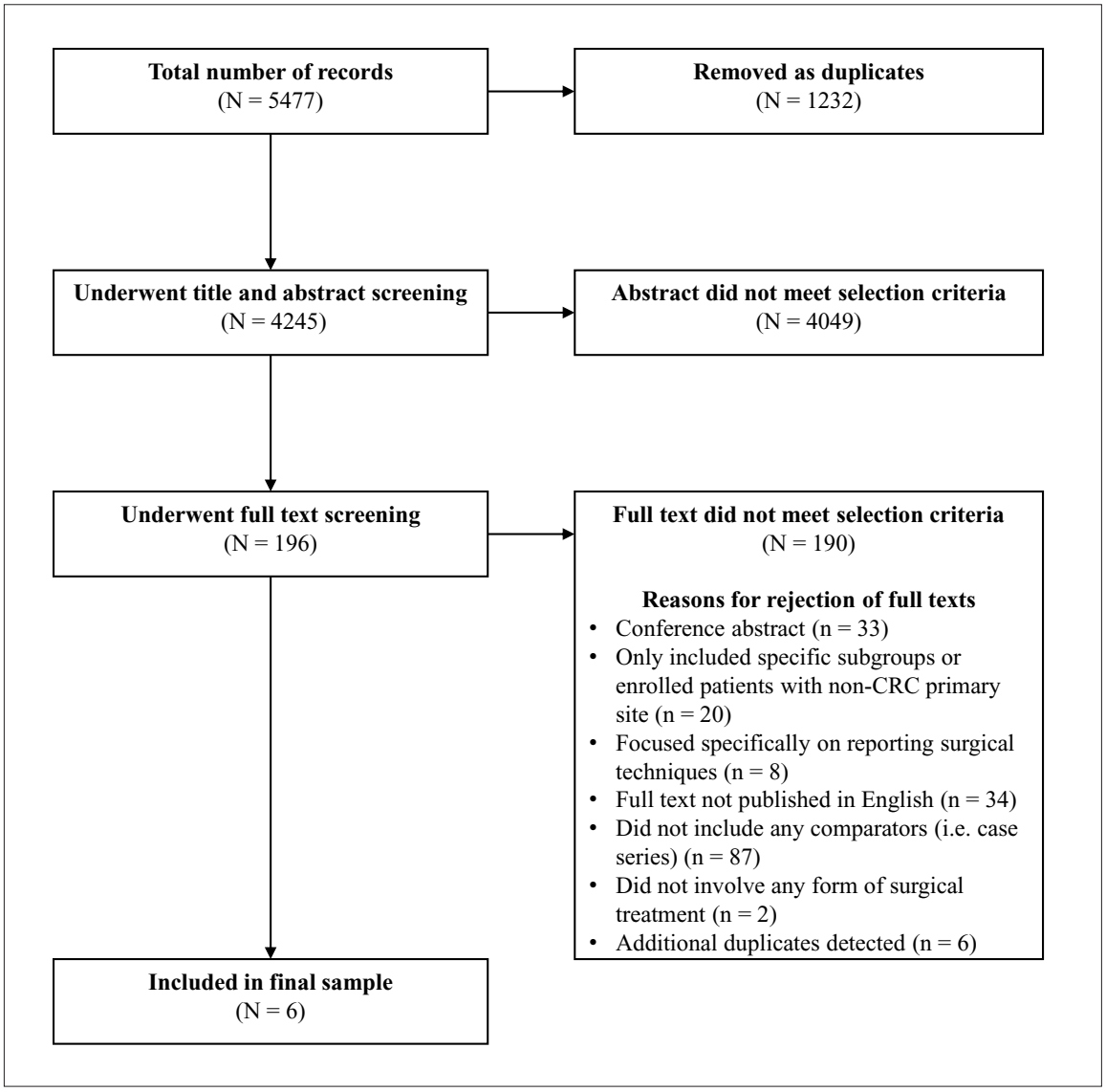

Fig. 1. PRISMA flowchart of article selection process.
CRC: colorectal cancer

Descriptive characteristics

Out of the 6 studies, 2 were randomised controlled trials (RCTs) and the remaining 4 were retrospective cohort studies.[10,11] The 2 RCTs were based on the same database, with Milosevic et al. adding 28 more patients to the original dataset.[11] In terms of comparators, 3 studies compared patients who underwent LUM to patients who did not, two studies compared patients who underwent LUM to LIM, and 1 study analysed both comparators. The sample sizes in the studies were mostly small, with the exception of Zong et al. who studied 1047 patients with CRC LUM.[12] With the exception of Iwasaki et al. who published their study in 2005, the publication dates were more recent for the rest of the included sample, ranging from 2015 to 2020.

No clear benefit in overall survival with LUM compared to no LUM

There were 4 studies that compared patients who underwent LUM versus no surgery, of which 2 were RCTs and the other 2 retrospective cohort studies. While the RCTs reported 5-year overall survival (OS), the retrospective studies analysed median OS. The RCTs included multiple variables for minimisation including CRC stage, prior liver resection, interval to surgery from diagnosis, and number of PM, creating balanced groups for randomisation. Both studies reported similar OS after LUM, with Treasure et al. reporting an estimated 5-year OS of 38.0% (95% confidence interval [CI] 23–62) for LUM group vs 29.0% (95% CI 16–52) in the control group.[10] Milosevic et al. reported an estimated

Table 1. Key characteristics and findings of the included studies

Reference	Publication year	Country of study	Sample size	Study design	Comparison group	Disease-free and/or overall survival	No. of pulmonary metastases	Time to surgery from diagnosis of CRC	No. of patients with chemotherapy	Inclusion of lung and liver metastasectomy
Treasure et al.[10]	2019	UK	65	RCT	Surgery versus no surgery	Estimated 5-year OS of 38.0% (95% CI 23.0–62.0%) for metastasectomy group Estimated 5-year OS of 29.0% (95% CI 16.0–52.0%) in control group HR for death within 5 years of 0.82 (95% CI 0.43–1.56)	Median of 2 pulmonary metastases (range 1–5) 14 (43.8%) solitary metastases in metastasectomy group 14 (42.4%) solitary metastases in control group	Median of 22.0 months (range 1.0–106.5) for metastasectomy group Median of 26.4 months (range 7.6–130.5) for control group	12 (37.5%) underwent chemotherapy in metastasectomy group 9 (27.3%) underwent chemotherapy in control group	Not included
Milosevic et al.[11]	2020	UK, Serbia	93	RCT	Surgery versus no surgery	Estimated 5-year OS of 36.4% (95% CI 21.3–53.0%) for metastasectomy group Estimated 5-year OS of 29.6% (95% CI 15.3–5.7%) for control group HR for death within 5 years of 0.87 (95% CI 0.51–1.48)	Median of 2 pulmonary metastases (range 1– 8) 18 (39.1%) solitary metastases in metastasectomy group 16 (34.0%) solitary metastases in control group	Median of 23.1 months for metastasectomy group Median of 27.4 months for control group Range not provided	19 (41.0%) underwent chemotherapy in metastasectomy group 23 (49.0%) underwent chemotherapy in control group	Not included
Zong et al.[12]	2020	China	17,776 (lung metastases 1,047; liver metastases 9,737)	Retrospective cohort	Surgery versus no surgery (subgroup comparison of lung metastasectomy versus liver metastasectomy) Both synchronous and metachronous metastases included in study	Surgery versus no surgery in patients with pulmonary metastases • Median OS of 38.0 months (range 26.5–49.5) for metastasectomy group • Median OS of 19.0 months (range 17.4–20.6) for no surgery group Lung versus liver metastasectomy • Median OS of 38.0 months (range 26.5–49.5) for lung metastasectomy group • Median OS of 30.0 months (range 28.0–32.0) for liver metastasectomy group	Not mentioned	Not mentioned	Not mentioned	Median OS of 16.0 months (range 12.1–19.9) with metastasectomy of both sites Median OS of 10.0 months (range 9.2–10.9) without metastasectomy

Table 1. Key characteristics and findings of the included studies (Cont'd)

Reference	Publication year	Country of study	Sample size	Study design	Comparison group	Disease-free and/or overall survival	No. of pulmonary metastases	Time to surgery from diagnosis of CRC	No. of patients with chemotherapy	Inclusion of lung and liver metastasectomy
Socola et al.[13]	2015	US	74 (underwent resection 28; did not undergo resection 46)	Retrospective cohort study	Surgery versus no surgery	Median OS of 53.0 months (range 43.8–62.2) for metastasectomy Median OS of 26.3 months (range 11.8–40.8) for non-surgery group	19 (68.0%) solitary metastases in surgery group 6 (13.0%) solitary metastases in non-surgery group 2 (7.0%) bilateral lung metastases in surgery group 40 (89.0%) bilateral lung metastases in non-surgery group	25 (89.0%) with metachronous metastases in surgery group 31 (67.0%) with metachronous metastases in non-surgery group Significant difference between both groups (P<0.05)	6 (21.0%) underwent chemotherapy with anti-EGFR monoclonal antibody in lung metastasectomy group 12 (26.0%) underwent chemotherapy with anti-EGFR monoclonal antibody in non-surgery group 12 (43.0%) underwent chemotherapy with bevacizumab in lung metastasectomy group 31 (67.0%) underwent chemotherapy with bevacizumab in non-surgery group	Not mentioned
Lee-Ying et al.[14]	2017	Canada	2,082 (lung metastases 41; liver metastases 168)	Retrospective cohort	Lung metastasectomy versus liver metastasectomy	Median OS of 42.8 months for lung metastasectomy Median OS of 48.0 months for liver metastasectomy No significant difference in median OS reported between groups (P=0.69)	Not mentioned	Time to surgery not mentioned 7 (17.1%) with synchronous metastases 34 (83.0%) with metachronous metastases	22 (54.0%) underwent chemotherapy in lung metastasectomy group 111 (66.0%) underwent chemotherapy in liver metastasectomy group	Excluded from study

Table 1. Key characteristics and findings of the included studies (Cont'd)

Reference	Publication year	Country of study	Sample size	Study design	Comparison group	Disease-free and/or overall survival	No. of pulmonary metastases	Time to surgery from diagnosis of CRC	No. of patients with chemotherapy	Inclusion of lung and liver metastasectomy
Iwasaki et al.[15]	2005	Japan	88 (lung metastases 48; liver metastases 32)	Retrospective cohort study	Lung metastasectomy versus liver metastasectomy	Estimated 5-year OS of 37.0% in lung metastasectomy group versus 42.8% in liver metastasectomy group (P=0.47) Disease-free survival of 947.06±840.39 days after lung metastasectomy versus 246.03±229.26 days after liver metastasectomy (P<0.01)	27 (56.3%) solitary metastases	All patients had metachronous metastases; synchronous metastases excluded as part of study criteria	40 (83.3%) underwent adjuvant chemotherapy in lung metastasectomy group 32 (87.5%) underwent adjuvant chemotherapy in liver metastasectomy group	Excluded from study

CI: confidence interval; CRC: colorectal cancer; EGFR: epidermal growth factor receptor; HR: hazard ratio; OS: overall survival; RCT: randomised controlled trial
Superscript numbers: Refer to numbers in REFERENCES

5-year OS of 36.4% (95% CI 21.3–53.0) for LUM group vs 29.6% (95% CI 15.3–45.7) in the control group.[1] The difference in OS with or without LUM was not statistically significant.

In the retrospective studies, Zong et al. reported median OS of 38 months (range 26.5–49.5) for LUM group vs 19 months (range 17.4–20.6) for patients who did not undergo surgery.[12] Socola et al. had better median OS of 53 months (range 43.8–62.2) for LUM group vs 26.3 months (range 11.8–40.8) for patients who did not undergo surgery.[13] Similarly, the difference in median OS were not statistically significant.

LUM is not associated with better overall survival compared to LIM

There is conflicting evidence in survival outcomes after LUM compared to LIM. Only retrospective data was available in this comparison. Out of the 3 studies, two showed worse OS in patients who undergo LUM, although they were not shown to be statistically significant.[2-4] Lee-Ying et al. reported median OS of 42.8 months after LUM compared to 48.0 months after LIM (P=0.69).[12,14,15] Similarly, Iwasaki et al. reported estimated 5-year OS of 37.0% after LUM vs 42.8% after LIM (P=0.46).[14] However, Zong et al. reported better survival after LUM, with a median OS of 38 months (range 26.5–49.5) after LUM versus 30 months (range 28.0–32.0) after LIM.[12]

LUM is associated with longer disease-free survival than LIM

Only 1 study, Iwasaki et al., reported disease-free survival (DFS). When compared to LIM, LUM was associated with significantly longer median DFS (947.06±840.39 versus 246.03±229.26 days, P<0.01).[15] Additional LUM for the patients who developed recurrence was not reported.

Patients who underwent LUM were more likely to have unilateral and solitary PM

Both RCTs included the number of PM in variables used for minimisation. They included 43.8% and 39.1% versus 42.4% and 34.0% of patients with solitary PM in the LUM and control group, respectively. The median number of metastases was 2, and ranged from 1 to 8 metastases.

Only 2 of the retrospective studies reported the number of PM in patients. In Socola et al., there were more patients with solitary PM that underwent LUM compared to those who did not (68.0% vs 13.0%).[13] No statistical analysis was provided. More patients (56.3%) who underwent LUM had solitary PM in the study by

Iwasaki et al. Only 1 study reported the incidence of bilateral PM.[13] Majority of patients who did not undergo surgery had bilateral PM (89.0% vs 7.0%). However, subsequent univariate analysis of prognostic factors in patients who underwent resection did not show any significant association of bilateral PM with survival (P=0.717).

Majority of patients who undergo LUM had metachronous PM

Time to LUM from diagnosis of CRC was not well reported in most studies. Majority of patients studied were those with metachronous PM. One study excluded patients with synchronous PM.[15] In patients who undergo LUM, majority present with metachronous PM.[13,14] Socola et al. also reported that significantly more patients with metachronous PM undergo LUM (89.0% versus 67.0%, P<0.05).[13]

For Treasure et al. and Milosevic et al., the median time to randomisation from diagnosis of CRC was also included into variables used for minimisation.[10,11] While the metastasectomy group had a shorter median duration by 4.3–4.4 months, this was not significant (22.0 and 23.1 months versus 26.4 and 27.4 months). However, it is worth noting that the shortest interval in the LUM group in Treasure et al. was 1 month.[10]

Large variation in uptake and regimens of postoperative chemotherapy for PM

The uptake of postoperative chemotherapy and types of chemotherapy regimens after metastasectomy differs widely between studies. There were 5 studies that reported on chemotherapy treatments. Uptake for postoperative chemotherapy was low in Treasure et al., with fewer patients in the control group undergoing chemotherapy (27.3% versus 37.5%).[10] Milosevic et al. reported higher postoperative chemotherapy rates overall, with more patients undergoing chemotherapy in the control group (41.0% versus 49.0%).[11] In 1 study, patients with more than Dukes A CRC were administered postoperative chemotherapy consisting tegaful and uracil (UFT) with leucovorin.[15] Majority of patients underwent this postoperative therapy in both LUM and LIM groups (83.3% and 87.5% respectively). Lee-Ying et al. reported postoperative chemotherapy in 54.0% of patients with LUM and a slightly higher rate of 66.0% in patients who underwent LIM.[14] While Socola et al. did not report actual proportion of patients who underwent chemotherapy, it was shown that bevacizumab was the most commonly used drug in both groups: n=12 (43.0%) and n=31 (67.0%) in LUM and no LUM group, respectively.[13]

The use of radiation therapy (RT) or radiofrequency ablation (RFA) in the treatment of PM was only described in the 2 RCTs.[10,11] Only a few patients (range 9–11) received RT during the 5-year follow-up period, of which half of the patients were from the control group. However, these numbers included RT for other locations of metastasis such as brain and bone.[10,11] The use of RFA was also very limited in these studies, and only 2–3 patients received RFA in both the control and LUM group[10,11] within 5 years of follow-up.

DISCUSSION

Pulmonary metastasectomy is regularly performed for a significant proportion of patients with metastatic CRC with PM, but is still lacking in quality evidence. Gonzalez et al. published a meta-analysis in 2013 looking at risk factors that affect survival after LUM, but only included retrospective single-arm studies.[16] In our study, we identified at least 195 studies about PM and LUM. Majority of the studies were removed due to the lack of comparators (e.g. case series). Out of the 6 remaining studies, 2 were based on the same RCT (PulMiCC), which was terminated early due to poor outcomes in the treatment group and worsening recruitment.

From our results, LUM does not show clear survival benefit at present. Studies that compared LUM against no surgery showed that patients who undergo LUM had better OS, although not statistically significant. The reported 5-year survival from the 2 RCTs was 36.0–38.0%, which was slightly lower than earlier reported 5-year survival of 40.0–60.0% based on case series and single-arm retrospective studies.[10,11] However, those who did not undergo surgery still had a 5-year OS of 29%, which is better than previously reported.[5] When compared against patients who undergo LIM, the results are less consistent. Two studies reported worse survival outcomes with LUM compared to LIM while another study reported otherwise; however, the results were not statistically significant. Even so, the reported survival outcomes for both LUM and LIM are better than those who do not undergo surgery. The reported 5-year survival of 37.0% after LUM is consistent with other studies.[10,11,15-17] Disease-free survival was only reported in a single study, which showed significantly better DFS with LUM. The time to recurrence was reported to be almost 3 times longer with LUM compared to LIM. This differs from several other large retrospective studies, which reported recurrence rates in LUM similar to that of LIM, with reported recurrence of up to 70.0–80.0% at 2 years.[18-20]

We also looked at several factors that may affect decision for LUM. In retrospective studies, patients with unilateral and solitary PM were more likely to undergo LUM. Only 7.0% of patients with bilateral PM underwent surgery in 1 study.[13] Other prognostic factors such as LUM resection margins and presence of hilar or mediastinal nodes were not available in these studies.

Majority of patients who undergo LUM also had metachronous metastases, which is consistent with other retrospective reviews that reflect better survival outcomes in patients who present with metachronous PM.[6,7,10,21] Survival data based on number of PM and metachronous presentation were not available based on these few reviews. In the meta-analysis by Gonzalez et al., shorter DFS was associated with increased mortality (hazard ratio [HR] 1.59, 95% CI 1.27–1.98). Similarly, multiple PM was associated with increased mortality (HR 2.04, 95% CI 1.72–2.41).[16] Chemotherapy is the main treatment for metastatic CRC, but uptake of adjuvant chemotherapy remains variable, ranging from 37.5–87.5%.[10,11,13,14] Reasons for no postoperative chemotherapy were not provided, and prior chemotherapy treatment were not available. There are currently no guidelines available on the duration of chemotherapy specifically for post-metastasectomy and would be an important aspect to address in the overall treatment of metastatic CRC.

Overall, the evidence suggests that there appears to be a role for LUM, but is limited by the quality of research available. Four out of 6 studies were retrospective in nature, with strong selection biases in decision for metastasectomy. Metastatic disease in CRC encompasses a spectrum of patients, and those who undergo LUM are likely to have more favourable patient and disease prognostic factors. Patients who are not fit to undergo chemotherapy or surgery, synchronous presentation, bilateral pulmonary tumours or multiple sites of metastases are less likely to undergo LUM. This selection bias was perhaps compounded by the lack of controlling for other confounders, including molecular status (such as BRAF, RAS and microsatellite instability).

While RCTs are ideal to overcome selection bias—the PulMiCC trial did include key variables for minimisation to allow for balanced groups to be studied—only 2 of the included studies in this review were RCTs, and both reflect the challenges of limited sample size in conducting a trial in such a complex group of patients. Of the 512 patients that were recruited at the first stage of the trial, 419 patients did not undergo randomisation. A subset of 155 patients were further studied on why randomisation did not proceed, and found that 56.0% were lost to randomisation due to clinical decisions from surgeons, oncologists and multidisciplinary tumour boards (MDT). In this trial, the main difficulty in recruitment was getting the clinician to relay the uncertainty of outcomes after LUM to both the patients and MDT, eventually succumbing to selection biases.

In addition, the confirmation of PM is tricky. Biopsy of pulmonary lesions can be challenging and are limited by its location, as well as its associated procedural risks. Diagnosis is henceforth made based on imaging findings, either at one sitting or over time. But, other differential diagnoses for such lung nodules may also include those of granulomas, primary lung cancers or other benign pathologies.

CONCLUSION

The benefit of LUM in metastatic CRC has not been well proven, despite being commonly performed. Our review shows that LUM failed to show any clear survival benefit when comparing LUM to LIM, and statistically non-significant marginal benefits when comparing to no surgery. We also showed that patients who underwent LUM in the included studies were likely to have a single tumour and have metachronous disease, highlighting the likelihood of selection biases in patient selection for LUM. Given the evidence available at present, we conclude that further prospective studies are needed to understand the true effect of LUM on outcomes in metastatic CRC.

REFERENCES

1. Misiakos EP, Karidis NP, Kouraklis G. Current treatment for colorectal liver metastases. World J Gastroenterol 2011;17:4067-75.
2. Vauthey J-N, Zorzi D, Pawlik TM. Making unresectable hepatic colorectal metastases resectable—does it work? Semin Oncol 2005;32:118-22.
3. Artigas V, Marín-Hargreaves G, Marcuello E, et al. [Surgical resection of liver metastases from colorectal carcinoma. Experience in Sant Pau Hospital]. Cir Esp (Engl Ed) 2007;81:339-44.
4. Weiser MR, Jarnagin WR, Saltz LB. Colorectal cancer patients with oligometastatic liver disease: what is the optimal approach? Oncology 2013;27:1074-8.
5. Mohammad WM, Balaa FK. Surgical management of colorectal liver metastases. Clin Colon Rectal Surg 2009;22:225-32.
6. Chakedis J, Schmidt CR. Surgical treatment of metastatic colorectal cancer. Surg Oncol Clin N Am 2018;27:377-99.
7. Mitry E, Guiu B, Cosconea S, et al. Epidemiology, management and prognosis of colorectal cancer with lung metastases: a 30-year population-based study. Gut 2010;59:1383-8.
8. Kanemitsu Y, Kato T, Hirai T, et al. Preoperative probability model for predicting overall survival after resection of pulmonary metastases from colorectal cancer. Br J Surg 2004;91:112-20.
9. Joanna Briggs Institute. Critical appraisal tools. Available at: https://jbi.global/critical-appraisal-tools. Accessed on 12 June 2021.

10. Treasure T, Farewell V, Macbeth F, et al. Pulmonary metastasectomy versus continued active monitoring in colorectal cancer (PulMiCC): a multicentre randomised clinical trial. Trials 2019;20:718.
11. Milosevic M, Edwards J, Tsang D, et al. Pulmonary metastasectomy in colorectal cancer: updated analysis of 93 randomized patients - control survival is much better than previously assumed. Colorectal Dis 2020;22:1314-24.
12. Zong Z, Zhou TC, Tang FX, et al. Impact of site-specific metastases on surgical value and survival among metastatic colorectal cancer patients. Am Surg 2020;86:220-7.
13. Socola F, Nguyen DM, Ochoa RE, et al. A cohort study evaluating the role of surgery for lung metastases from colorectal cancer. Anticancer Res 2015;35:3431-5.
14. Lee-Ying R, Bernard B, Gresham G, et al. A comparison of survival by site of metastatic resection in metastatic colorectal cancer. Clin Colorectal Cancer 2017;16:e23-8.
15. Iwasaki A, Shirakusa T, Yamashita Y, et al. Characteristic differences between patients who have undergone surgical treatment for lung metastasis or hepatic metastasis from colorectal cancer. Thorac Cardiovasc Surg 2005;53:358-64.
16. Gonzalez M, Poncet A, Combescure C, et al. Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. Ann Surg Oncol 2013; 20:572-9.
17. Girard P, Ducreux M, Baldeyrou P, et al. Surgery for lung metastases from colorectal cancer: analysis of prognostic factors. J Clin Oncol 1996;14:2047-53.
18. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol 2007;25:4575-80.
19. Tampellini M, Ottone A, Bellini E, et al. The role of lung metastasis resection in improving outcome of colorectal cancer patients: results from a large retrospective study. Oncologist 2012;17:1430-8.
20. Sakamoto T, Tsubota N, Iwanaga K, et al. Pulmonary resection for metastases from colorectal cancer. Chest 2001;119:1069-72.
21. Aberg T. Selection mechanisms as major determinants of survival after pulmonary metastasectomy. Ann Thorac Surg 1997;63:611-2.

COMMENTARY

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Integrating mental healthcare in primary care in Singapore

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Management of mental health conditions can be both resource-intensive and costly. The rigour of obtaining appointments and the long waiting time at tertiary hospitals, coupled with the need to obtain leave from work form a significant financial and logistical burden on patients for the treatment of mental health conditions. The alternative—more flexible private practice appointments—comes with a high consultation fee. The direct costs (e.g. medication and consultation fees) are eclipsed by the indirect costs (e.g. loss of wages), with over 80% of the annual total cost attributed to indirect cost.[1] Moreover, patients with mental health conditions often have comorbid physical conditions,[2] and would benefit from holistic co-management of these conditions.

The World Health Organization asserted that integrating mental health into primary care settings would produce clear benefits, such as increased access and affordability.[3] Singapore has taken steps to integrate mental health services into primary care.

Singapore's National Mental Health Blueprint was initiated in 2007 to improve mental health services. It was centred around integrating mental health services, improving mental health literacy, and developing workforce and research capabilities in community-based services. Consequently, the 2012 Community Mental Health (CMH) Masterplan proposed the need to lend importance to treating mental health conditions within the community, focusing on early detection and patients with stable, chronic mental health conditions.

In line with these plans is the Ministry of Health's healthcare vision for "One Singaporean, One Family Doctor". It focuses on each Singaporean being in a long-term partnership with a family doctor, and emphasises preventative and community care. This vision enables the primary care ecosystem to integrate mental health and physical health through increased capability and capacity of care access.

Capability and capacity alone are insufficient. The direct and indirect costs of mental healthcare are high, with conditions such as depressive disorder costing patients over USD7,500 (SGD10,000) per year in 2008.[1] The plans highlighted in the CMH Masterplan would require improving the affordability of mental health services to ensure these are accessible to all. Singapore operates on a copayment model: a combination of government subsidies, patient's out-of-pocket expenditure, and mandatory national savings such as the MediSave Scheme,[4] which helps all individuals save a portion of their pension for medical expenses. Subsidies are disbursed through schemes such as the Community Health Assist Scheme (CHAS) and the Chronic Disease Management Programme (CDMP).[5] Mental health conditions with treatments that are covered by these schemes in primary care settings include schizophrenia, major depression, bipolar disorder and anxiety.

There are 2 main ways patients can access mental health services in primary care, via private general practitioner (GP) clinics or publicly funded polyclinics (Fig. 1).

The first way patients can access mental healthcare is through the Mental Health GP Partnership Programme (MHGPP). Piloted in 2003 by the Institute of Mental Health, the MHGPP's main goal was to identify, train and collaborate with GPs. The GP partners assisted in managing patients with stable mental health conditions whose diagnoses were covered under the CDMP Mental Illness scheme, such as depression, anxiety and schizophrenia.

During the pilot process, key issues were identified, such as GPs' lack of confidence in treating mental health conditions and the affordability of psychotropic drugs.[6] These issues have since been addressed through refresher sessions carried out for GP partners and centralised drug support arrangements for affordability.[7] GPs are also invited to attend regular case discussions and engagement sessions held by the mental health services housed in tertiary care facilities.

Since then, the focus of the MHGPP model of care has evolved. Currently, GPs not only manage stable patients right-sited from hospitals but also act as gatekeepers to other mental health services. They can consult new walk-in cases, manage patients within their scope of practice, and refer any patients with severe symptoms or conditions not covered by the MHGPP to a partnered

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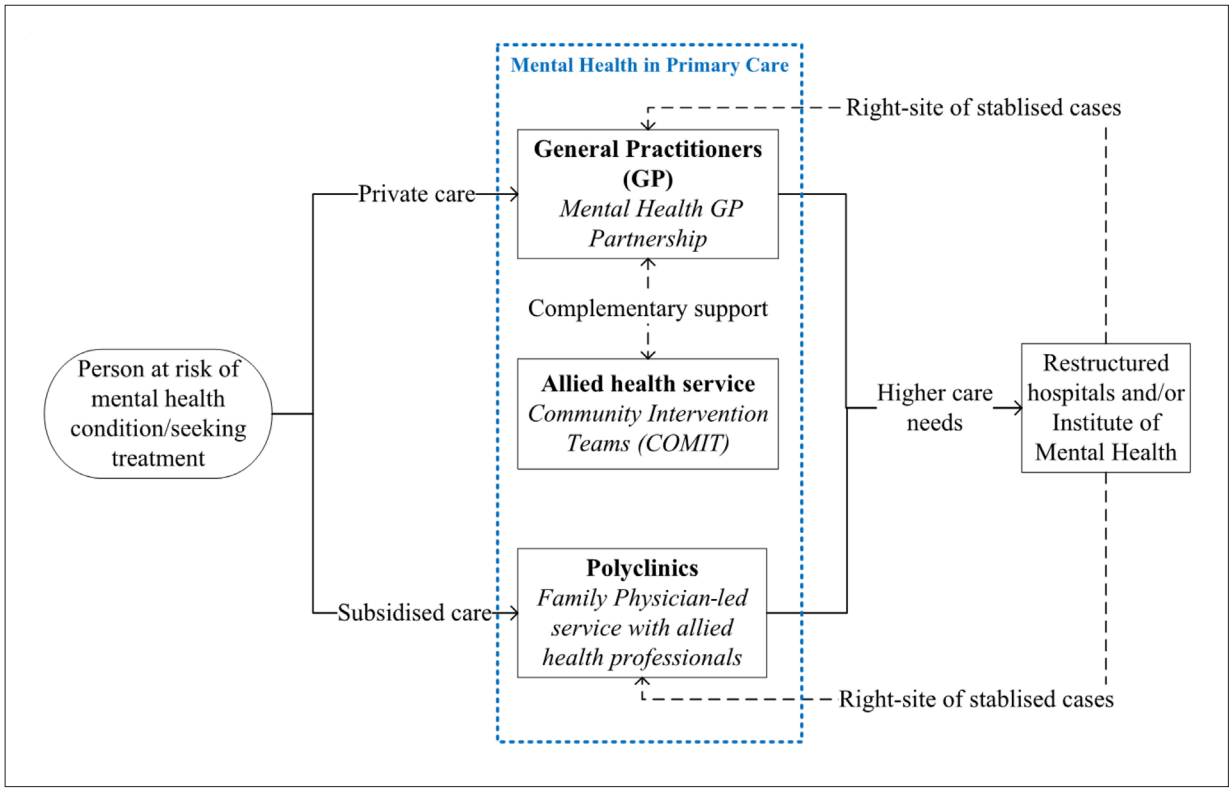

Fig. 1. Mental health services in the primary care setting.

hospital for follow-up. Additionally, the MHGPP has scaled up to affiliate with all public acute hospitals. In 2010, the MHGPP included 40 GPs, with 200 patients successfully right-sited from public hospitals. In 2021, there are now over 200 GPs and over 1,500 patients seen annually, identified through early detection and diagnosis by GPs.

The MHGPP model of care does not operate in isolation. Following the CMH Masterplan in 2012, the Community Intervention Team (COMIT) was developed as a complementary service within the primary care ecosystem. COMIT is an allied health-led team embedded in the community, which offers services to complement the pharmacological interventions provided by GPs. The ecosystem allows for constant information flow and a feedback loop between COMIT and GPs, with GPs able to receive updates on the patient's care from allied health professionals. Besides supporting psychological interventions, COMIT also provides social services, which help mitigate family stressors contributing to mental health issues.

The second avenue for patients to access mental health services in primary care is through polyclinics. Unlike GP clinics that are standalone practices, polyclinics house multiple services such as outpatient medical care and health screenings under one roof. Additionally, unlike GPs in the MHGPP who attend short clinical attachments or refresher courses, family physicians at polyclinics attend clinical attachments, co-consultation with psychiatrists, and monthly multidisciplinary case discussions. Similar to GPs, polyclinics serve a gatekeeping function by referring patients to hospitals for follow-ups. Polyclinics serve an additional function for patients requiring government subsidies, as assessment and referral from a polyclinic is the only route for eligibility to receive subsidised mental healthcare in hospitals. For patients not requiring hospital referrals, doctors in the polyclinics could also refer patients to in-house psychological services.

Polyclinics' mental health capability and capacity have increased over the years. Family physicians and allied health teams provide assessment, diagnosis and management of patients with mild to moderate mental health conditions. Psychological services were uncommon in polyclinic settings before the CMH Masterplan in 2012. In an effort to improve access, the CMH Masterplan was enhanced in 2017 to increase capabilities of polyclinics further. The plan: for 1 in 2 polyclinics to have mental health clinics by 2021. Today, Singapore has achieved this target, with 16 out of 20 polyclinics providing mental health and/or dementia care to over 9,500 patients to date. This demonstrates

primary care's role in early identification that helps relieve strain on hospital resources and ensure better utilisation of healthcare resources.

Despite the strides that have been made to integrate mental healthcare into primary care, barriers to success still exist. Singapore aims to further improve access to mental healthcare in the coming years. Apart from planning, there is a need to shape an open society that is accepting of mental health conditions, to allow those who require assistance to access services without stigma. There is still prevailing stigmatisation of people with mental health conditions in Singapore, evident through negative images portrayed in the media and social rejection. There appears to be a lack of awareness on some mental health conditions such as obsessive-compulsive disorder (28.7%) compared to depression (55.2%).[8] Public education via campaigns to debunk myths or misconceptions, and increase awareness of mental health is a preliminary step that has seen short-term success.[9] In 2018, Singapore's National Council of Social Services launched the "Beyond the Label" movement—a 5-year effort to address stigma and go beyond a person's diagnosis. However, it is necessary to examine in detail the effectiveness of these campaigns, for enhancement to ensure that further large-scale campaigns can meet the goals of long-term anti-stigma efforts. There is a lack of peer-reviewed research regarding anti-stigma work in Singapore, and encouraging structured research and publication would allow for evaluations and improvements for future campaigns.[10]

Reviews of the integrated care landscape are also pertinent for continued improvements. Singapore could look to the Brown Primary Care Initiative, which places the GP at the forefront of patient care,[11] following the Patient-Centered Medical Home (PCMH) model. This model also suggests that technology can drive improved mental health management in primary care settings. The PCMH model utilises telemedicine to assist GPs in managing their mental health cases. Singapore is already making strides in this direction, and in COVID-19, polyclinic psychological services offered teleconsultations to patients. Singapore is also exploring how telemedicine can help increase the range of conditions that GPs can oversee, as well as to allow for support and a second opinion for GPs seeking advice. With further developments, telemedicine as a whole could provide a new, more accessible channel for those currently unable to receive mental healthcare through traditional services.

Singapore is making strides to integrate mental health into primary care, with multiple access points to mental health services in the community.

REFERENCES

1. Ho RC, Mak KK, Chua AN, et al. The effect of severity of depressive disorder on economic burden in a university hospital in Singapore. Expert Rev Pharmacoecon Outcomes Res 2013;13:549-59.
2. Goldman LS. Comorbid medical illness in psychiatric patients. Curr Psychiatry Rep 2000;2:256-63.
3. World Health Organization and World Organization of Family Doctors. Integrating mental health into primary care: a global perspective. Geneva 2008.
4. Central Provident Fund Board. MediSave. Available at: https://www.cpf.gov.sg/Members/Schemes/schemes/healthcare/medisave. Accessed on 4 August 2021.
5. Ministry of Health Singapore. Chronic Disease Management Programme (CDMP). Available at: https://www.moh.gov.sg/policies-and-legislation/chronic-disease-management-programme-(cdmp). Accessed on 4 August 2021.
6. Lum AW, Kwok KW, Chong SA. Providing integrated mental health services in the Singapore primary care setting – the general practitioner psychiatric programme experience. Ann Acad Med Singap 2008;37:128-31.
7. Lum WMA, Chew J, Lim BL. The successful collaboration between psychiatrists, a mental health institution and general practitioners in primary care. Singapore Fam Phys 2010;36:19-21.
8. Chong SA, Abdin E, Picco L, et al. Recognition of mental disorders among a multiracial population in Southeast Asia. BMC Psychiatry 2016;16:121.
9. Thornicroft G, Mehta N, Clement S, et al. Evidence for effective interventions to reduce mental-health-related stigma and discrimination. Lancet 2016;12;387:1123-32.
10. Kuek JH, Chen SY, Chua HC. The Need for Scholarly Evaluation of Programmes Targeting Mental Health Stigma in Singapore. Ann Acad Med Singap 2019;48:330-2.
11. Parker DR, Goldman RE, Brown J, et al. The Brown Primary Care Initiative design for strategies towards patient-centered medical home practice transformation. Primary Health Care 2014;4:1-7.

LETTER TO THE EDITOR

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Treatment of Ewing sarcoma in children: Results from a single centre

Dear Editor,

Ewing sarcoma is a malignant mesenchymal tumour that presents as a bone or soft-tissue sarcoma. Translocations involving the *EWS* gene on chromosome 22q12 are unique molecular signatures.[1,2] Compared with the West where the annual incidence is 1–3 per million, incidence has been reported to be lower among Asians[1] and in East Asia.[3] Paediatric-specific management and outcome data are distinctively absent in this region, which prompted the report of our experience herein.

This is a retrospective chart review of all paediatric patients treated for Ewing sarcoma from 2008 to 2020 at our institution, the Mount Elizabeth Hospital in Singapore. Their clinical, histopathological, treatment and follow-up data were summarised. Survival was measured from diagnosis and censored at the end of May 2021 or upon death. A literature search from PubMed was conducted using the search terms: ((Ewing sarcoma) AND (child OR pediatric)) AND (China OR Hong Kong OR Japan OR Korea OR Taiwan OR Thailand OR Singapore) AND Treatment. These countries/territories were selected as they represented the regions where childhood oncology studies were most often reported in East Asia and Southeast Asia. The search results were screened to include only clinical studies with at least 10 subjects involving children (≤18 years old). Approval from institutional review board was not required for observational studies outside the context of a clinical trial in our institution.

Ten children were treated for histopathology confirmed Ewing sarcoma during the study period (Table 1), with mean age of 7.0 (range 2.2–16.8) years. Eight (80%) of the children were boys. *EWS-FLI1* transcript was tested by fluorescence in situ hybridisation in 8 cases and all were positive. Eight had skeletal primaries (femur, 4; chest wall, 2; tibia, 1; skull base, 1), while 2 had lung tumour as the extraskeletal primary. Seven children presented with localised disease while 3 had metastatic disease. All patients were from Asia (Bahrain, 2; Bangladesh, 1; China 4; Singapore, 1; Vietnam, 2). Seven patients were treatment naive while 3 had received neoadjuvant chemotherapy from other centres before they came to our hospital for surgery and postoperative management. At a median follow-up of 3.1 (range 0.5–12.9) years, 9 were surviving in first complete remission and 1 died of the disease, yielding an overall and event-free survival of 88.9%.

Six children (localised, 4; metastatic, 2) were treated according to the European Ewing tumour Working Initiative of National Groups (Euro-E.W.I.N.G.) protocol with 5 cycles of vincristine, ifosfamide, doxorubicin and etoposide (VIDE) as induction chemotherapy. Complete resection of primary tumour was achieved in 1 patient at diagnosis, 4 after neoadjuvant therapy, while the 1 patient with skull base tumour had complete resolution of the disease on chemotherapy alone. Among the 4 surgical specimens obtained after chemotherapy, 2 had tumour necrosis of 90–99% and the other 2 had complete necrosis. All 6 patients were surviving in complete remission.

Four children received neoadjuvant chemotherapy according to the US Children's Oncology Group (COG) protocol with vincristine, doxorubicin, cyclophosphamide, and alternating with ifosfamide and etoposide (VDC-IE) on 2-week cycles. Histopathology showed tumour necrosis of <90% in all cases. Three of them were surviving, with 2 in complete remission and 1 with disease in metabolic remission. The other patient relapsed and died at 1.1 years after diagnosis.

The literature search done in May 2021 obtained 280 articles. Eleven studies were finally identified (materials available on request). All were retrospective studies. They originated from China (n=3), Japan (n=5), Korea (n=1) and Taiwan (n=2). None was reported from Hong Kong, Singapore or Thailand. None of the studies was specific for children, and all were combined paediatric and adult series. All followed international protocols with combined modality treatment comprising all 3 modalities: chemotherapy, surgery and radiotherapy. The chemotherapy regimens used were quite variable even within the same studies, but VDC-IE appeared to be the most popular regimen. Survival rates were 5.9–78.3%. Notably, from the 2 largest series of publications, younger patients fared better in terms of long-term event-free survival.[6,7]

Prior to the era of chemotherapy, 90% of patients with localised Ewing sarcoma died from the disease after local therapy alone.[1] Hence, systemic chemotherapy and local treatment (surgery and/or radiotherapy) are both indispensable in the contemporary management of Ewing sarcoma. Prognostic factors are influenced by age, tumour extent or volume, stage of the disease, success of local therapy, but histological response with ≥90% of tumour necrosis is the strongest predictor for long-

Table 1. Summary of the clinical features, treatment and outcomes of the 10 paediatric cases of Ewing sarcoma

	Sex/age, years	Primary site and metastasis	Radiotherapy	Histologic response[a]	Postoperative treatment and outcomes
Initial chemotherapy according to the Euro-E.W.I.N.G. protocol (VIDE)[b]					
1	Male/10.9	Chest wall, left; localised	Nil	90–99% necrosis	VAI followed by VAC; alive without disease at 12.9 years
2	Male/12.5	Femur, left; metastatic to lungs, lymph nodes, both testes, bone marrow	Abdominal and right inguinal regions	100% necrosis	Consolidation with high-dose busulfan and melphalan followed by autologous stem cell rescue; alive without disease at 10.5 years
3	Male/6.5	Skull base-cavernous sinus, left; localised, underlying NF-1	Primary	NA; complete resolution after chemotherapy	VAI followed by VAC; alive without disease at 5.6 years
4	Male/3.0	Chest wall, right; localised	Nil	NA; complete resection at diagnosis	VAI followed by VAC; alive without disease at 5.3 years
5	Female/2.7	Lung, right; localised	Nil	100% necrosis	VAI followed by VAC; alive without disease at 2.4 years
6	Male/16.8	Femur, left; metastases to right lung	Primary	90–99% necrosis	VAI followed by VAC; alive without disease at 0.5 year; on postoperative chemotherapy
Initial chemotherapy according to the US Children's Oncology Group protocol (VDC-IE)[c]					
7	Male/2.2	Tibia, left; localised	Primary	51–89% necrosis	VAI followed by VAC; alive without disease at 3.1 years
8	Male/2.8	Femur, left; localised	Primary	51–89% necrosis	VAI followed by VAC; alive without disease at 2.9 years
9	Male/1.6	Femur, right; localised	Primary	51–89% necrosis	VAI followed by VAC; relapsed and died of disease at 1.1 years
10	Female/11.1	Lung, left; metastases to both lungs	Nil	≤50% necrosis	Various regimens; alive with metabolically inactive disease at 1.3 years; on maintenance treatment with pazopanib

Euro-E.W.I.N.G.: European Ewing tumour Working Initiative of National Groups; NA: not available; NF-1: neurofibromatosis type 1; VAC: vincristine + actinomycin D + cyclophosphamide; VAI: vincristine + actinomycin D + ifosfamide; VDC-IE: vincristine, doxorubicin + cyclophosphamide alternating with ifosfamide + etoposide; VIDE: vincristine + ifosfamide + doxorubicin + etoposide

[a] The histologic response was graded into 4 categories: ≤50% necrosis, 51–89%, 90–99% and 100% necrosis.[4]

[b] The Euro-E.W.I.N.G. protocol was the default in-house regimen for the treatment of Ewing sarcoma.

[c] The Children's Oncology Group protocol was used in patients 7, 8 and 9 before they came to our hospital for further treatment. Patient 10 received this protocol, as emerging evidence suggested this to be a superior regimen;[5] a different regimen was used postoperatively in view of the suboptimal response on histology.

[4,5] Refer to REFERENCES

term survival.[2] Hence, the importance of an effective chemotherapeutic regimen cannot be overemphasised.

Current chemotherapeutic regimens that are highly effective for Ewing sarcoma are pioneered by intergroup collaborations in both Europe and North America. The Euro-E.W.I.N.G. 99 was the first intergroup regimen in Europe. The protocol uses vincristine, ifosfamide, doxorubicin, etoposide, cyclophosphamide and dactinomycin in various combinations at 3-week intervals over 42 weeks as the treatment backbone.[8] The COG protocol uses vincristine, doxorubicin and cyclophosphamide, alternating with ifosfamide and etoposide (VDC-IE) at 2-week intervals over 28 weeks.[9] However, the COG chemotherapeutic regimen has been considered too harsh in some Asian countries.[10] Among the studies identified from the literature search that mentioned the use of VDC-IE,[11,12] the alternating cycles were administered at 3-week intervals, with a total duration of treatment of 42 weeks. This might have been one of the contributing factors for the generally inferior treatment outcomes observed in Asian patients with Ewing sarcoma, which deserves further study.

From our experience, based on the extent of tumour necrosis after induction treatment, the Euro-E.W.I.N.G. regimen seems to be equally effective in Asia compared with the COG protocol. However, the number of patients is small. More studies from East Asia and Southeast Asia are needed to inform paediatric oncologists on the optimal management of childhood Ewing sarcoma, including the level of supportive care required. Given the rarity of the disease in this part of the world, international collaboration is clearly indicated.

REFERENCES

1. Hesla AC, Papakonstantinou A, Tsagkozis P. Current status of management and outcome for patients with Ewing sarcoma. Cancers (Basel) 2021;13:1202.
2. DuBois SG, Dirksen U. Contemporary approach to therapy for Ewing sarcoma. In: Arndt CA (Ed). Sarcomas of bone and soft tissues in children and adolescents. 1st Ed. Cham: Springer Nature Switzerland AG; 2021.
3. Fukushima T, Ogura K, Akiyama T, et al. Descriptive epidemiology and outcomes of bone sarcomas in adolescent and young adult patients in Japan. BMC Musculoskelet Disord 2018;19:297.
4. Wunder JS, Paulian G, Huvos AG, et al. The histological response to chemotherapy as a predictor of the oncological outcome of operative treatment of Ewing sarcoma. J Bone Joint Surg Am 1998;80:1020-33.
5. Wheatley K, Moroz V, Marec-Berard, et al. First results of the Euro Ewing 2012 trial comparing two chemotherapy regimens in newly diagnosed Ewing sarcoma. Presented at the Connective Tissue Oncology Society Annual Meeting, 13-16 November 2019, Tokyo, Japan.
6. Obata H, Ueda T, Kawai A, et al. Clinical outcome of patients with Ewing sarcoma family of tumors of bone in Japan: the Japanese Musculoskeletal Oncology Group Cooperative Study. Cancer 2007;109:767-75.
7. Lee JA, Kim DH, Cho J, et al. Treatment outcome of Korean patients with localized Ewing sarcoma family of tumors: a single institution experience. Jpn J Clin Oncol 2011;41:776-782.
8. Le Deley MC, Paulussen M, Lewis I, et al. Cyclophosphamide compared with ifosfamide in consolidation treatment of standard-risk Ewing sarcoma: results of the randomized noninferiority Euro-EWING99-R1 trial. J Clin Oncol 2014;32:2440-8.
9. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. J Clin Oncol 2012;30:4148-54.
10. Totadri S, Bansal D, Rao KLN, et al. Challenges in the management of localized Ewing sarcoma in a developing country. Pediatr Hematol Oncol 2020;37:610-9.
11. Xie CF, Liu MZ, Xi M. Extraskeletal Ewing's sarcoma: a report of 18 cases and literature review. Chin J Cancer 2010;29:420-4.
12. Lee CY, Yen CC, Yen HJ, et al. Outcomes of 50 patients with Ewing sarcoma family of tumors treated at a single institution in Taiwan. Medicine 2016;95:e3830.

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LETTER TO THE EDITOR

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Chorea precipitated by phototherapy as initial presentation of systemic lupus erythematosus

Dear Editor,

Chorea is a well-recognised albeit rare neuropsychiatric manifestation of systemic lupus erythematosus (SLE). We describe here a case of a 67-year-old woman presenting with chorea, which affected her left lower limb and both upper limbs after phototherapy.

Chorea is an extrapyramidal movement disorder characterised by non-repetitive, abrupt, involuntary jerky movements that may be unilateral or generalised. The movements are non-patterned with variable speed, timing and direction, flowing from one body part to another and giving, in less severe cases, an appearance of fidgetiness. The unpredictable nature of chorea distinguishes it from tremor and dystonia.[1] Chorea has numerous aetiologies, including structural, pharmacologic, autoimmune, metabolic and genetic. SLE is one such cause and the systemic autoimmune disorder is characterised by the presence of autoantibodies and multiorgan involvement. Neuropsychiatric symptoms are recognised manifestations of SLE and are included in classifications by the American College of Rheumatology (ACR), European League against Rheumatism (EULAR-ACR 2019) and Systemic Lupus International Collaborating Clinics (SLICC 2012). Chorea is the most common movement disorder in patients with SLE, with prevalence around 1–3%.[2-4] While phototherapy has been reported to precipitate SLE,[5,6] chorea as first presentation of SLE consequent to phototherapy has not been reported in medical literature.

We discuss the case of a 67-year-old woman with a background of quiescent rheumatoid arthritis presenting with choreoathetoid movements. The symptoms started 2 weeks after initiation of phototherapy for presumptive asteatotic eczema over her chest. She underwent a total of 5 sessions of narrow-band ultraviolet B (UVB) phototherapy, from 700mJ to 1,000mJ over 4 weeks. She did not have phototherapy prior to this episode. The movements initially involved her left lower limb, then progressed to both upper limbs, affecting the left more than the right. She also developed a photosensitive rash. She had no oral ulcers, joint pains or constitutional symptoms. There was no weakness or numbness, seizures, psychosis nor cognitive impairment. She had no previous history of diabetes mellitus or thyroid illness. She had no family history of movement disorders, dementia or autoimmune conditions. Examination reviewed erythema of the face sparing the eyes (where the protective goggles were worn during phototherapy). There were involuntary, variable, abrupt and rapid movements of her left upper and both lower limbs. Limb power and sensation were both preserved. Examination of the cranial nerves and gait was unremarkable. There were no cortical or cerebellar signs.

Her blood work showed anaemia (haemoglobin 10.0g/dL) and leukopaenia (white blood cells $3.66x10^9$/L) with no evidence of haemolysis. Vitamin B12 levels were slightly low at 139pmol/L. Haemoglobin A1c and glucose levels were normal. C-reactive protein was high at 104mg/L, compared to previous level (3.4mg/L) done during her rheumatoid follow-up. Antinuclear antibody was homogeneous with a titre of >1/640. Anti-double-stranded DNA antibody was raised at 137 IU (>30 IU considered positive), while C3 and C4 levels were low at 0.33g/L (normal: 0.90–1.80g/L) and 0.02g/L (0.10–0.40g/L), respectively. Anti-Ro and Anti-La antibodies were raised at 4.8U and 1.1U, respectively. Schirmer's test was negative. While chorea in SLE is strongly associated with antiphospholipid antibodies (aPL),[7] she tested negative for lupus anticoagulant (LAC), anticardiolipin (aCL) and anti-B2 glycoprotein antibodies. Her previous autoimmune workup and complement level were normal before current admission.

Brain magnetic resonance imaging (MRI) showed scattered fluid attenuated inversion recovery (FLAIR) hyperintensities in the bilateral periventricular subcortical white matter. Magnetic resonance angiogram did not show any evidence of vasculitis nor any abnormalities of intracranial vasculature (Fig. 1). Lumbar puncture showed normal biochemistry (white blood cells 2/mL, red blood cell 0/mL, protein 0.31g/L, glucose 2.5mmol/L). Cerebrospinal fluid cultures, autoimmune panel and anti-B2 glycoprotein were negative. Malignancy screen (including mammography, computed tomography scan of thorax, abdomen and pelvis and serum paraneoplastic panel) was unyielding. EEG showed no epileptiform activity. A skin biopsy of her chest rash was positive for dermo-epidermal junction immunoreactivity with IgM and C3, consistent with lupus erythematosus.

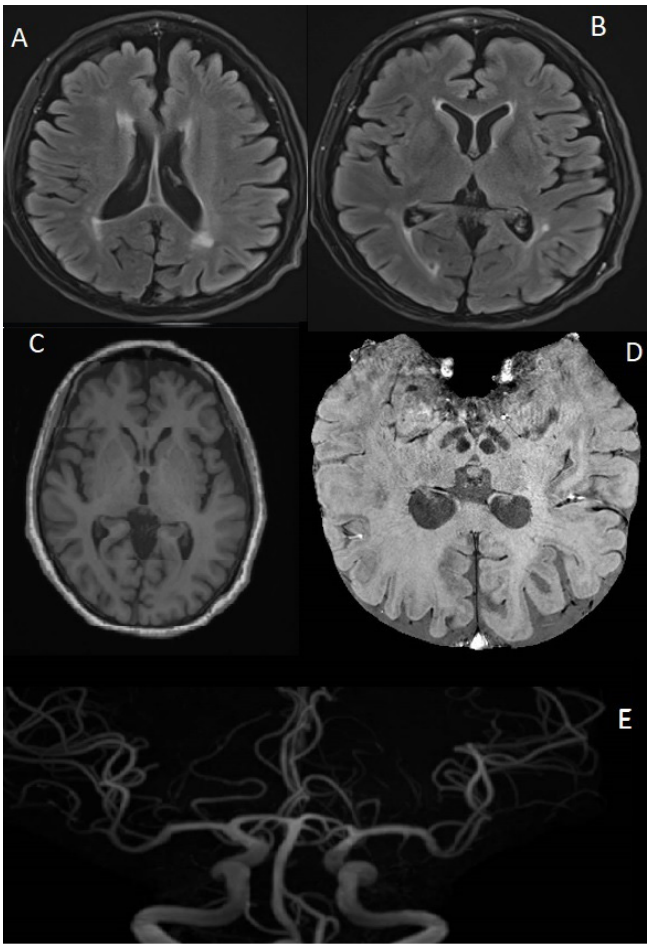

Fig. 1. The magnetic resonance brain images show periventricular white matter hyperintensities in the fluid attenuated inversion recovery setting (A and B), which is a common finding of neuropsychiatric systemic lupus erythematosus. The bilateral caudate nuclei and basal ganglia are within normal limits on T1-weighted image (C) and the nigrosome-1 is preserved on both sides on the susceptibility map-weighted image (D). The magnetic resonance angiogram shows no evidence of beading suggestive of vasculitis (E).

Tetrabenazine and olanzapine were started for symptomatic relief with some improvement in chorea. She responded well to hydroxychloroquine, methylprednisolone and cyclophosphamide with complete resolution of chorea after 2 days.

Her case is a novel description of SLE first presenting with phototherapy-precipitated chorea. Past reports have described phototherapy precipitating SLE manifestations involving the skin and joints as the presenting symptoms.

Ultraviolet radiation (UVR) is known to trigger cutaneous lupus erythematosus (CLE), with photosensitivity comprising one of the ACR diagnostic criteria for SLE.[8] While the mechanisms of CLE continue to be elucidated, it is believed to be the manifestation of similar pathologic mechanisms involved in systemic disease with autoantibodies and immune complexes causing tissue damage. UVR promotes development of cutaneous lesions by augmenting apoptotic cells by lymphocytic recruitment and antibody-mediated cytotoxicity.[9]

While cutaneous eruptions secondary to photosensitivity after exposure to ultraviolet radiation, in particular UVB (medium wavelength, 280 to 315nm) is well recognised in literature, the relationship between cutaneous UVB exposure and systemic SLE flares are only anecdotal and suggested in case reports. Fruchter et al.[5] described the clinical presentation of inflammatory polyarthropathy and urticarial vasculitis associated with haematological abnormalities as first presentation of SLE, following ultraviolet radiation in an artificial tanning device manufactured in recent years to produce higher levels of UVB. Pirner et al.[6] also reported in earlier years the development of photosensitive rash and arthritis associated with haematological derangements consistent with the diagnosis of SLE in a patient who received psoralen and ultraviolet A therapy for psoriasis. Our case further supports the possible pathogenic role of ultraviolet exposure in systemic SLE flares.

Among the neurological manifestations of SLE, chorea is rare. Although chorea usually occurs during the course of SLE, it may also be the presenting feature of the illness, sometimes preceding other symptoms by several years. Chorea in SLE has been strongly associated with antiphospholipid antibodies, namely LAC, aCL and anti-B2 glycoprotein 1 antibodies. Given the low prevalence of chorea at 2% in SLE (1.3% in antiphospholipid syndrome),[7] a high index of suspicion is required to enable early diagnosis and prompt treatment to prevent further symptoms and complications related to the autoimmune process. Neuroimaging can provide further insight and assist with diagnosis of neuropsychiatric lupus. One of the most common MRI findings of neuropsychiatric SLE is periventricular white matter hyperintensities in T2 and FLAIR images,[10] as in our case (Fig. 1).

REFERENCES

1. Cardoso F, Seppi K, Mair J, et al. Seminar on choreas. Lancet Neurol 2006;5:589-602.
2. Joseph FG, Lammie GA, Scolding NJ. CNS lupus: a study of 41 patients. Neurology 2007;69:644-54.

3. Spinosa MJ, Bandeira M, Liberalesso PB, et al. Clinical, laboratory and neuroimage findings in juvenile systemic lupus erythematosus presenting involvement of the nervous system. Arq Neuropsiquiatr 2007;65:433-9.
4. Cervera R, Asherson RA, Font J, et al. Chorea in the antiphospholipid syndrome. Clinical, radiologic, and immunologic characteristics of 50 patients from our clinics and the recent literature. Medicine (Baltimore) 1996;76:203-12.
5. Fruchter O, Edoute Y. First presentation of systemic lupus erythematosus following ultraviolet radiation exposure in an artificial tanning device. Rheumatology (Oxford) 2005;44:558-9.
6. Pirner K, Rubbert A, Salinger R, et al. Bedeutung des UV-Lichtes in der Pathogenese des SLE: Kasuistik und Diskussion der Literatur [Significance of ultraviolet light in the pathogenesis of systemic lupus erythematosus: case report and discussion of the literature]. Z Rheumatol 1992;51:20-4.
7. Ricarte IF, Dutra LA, Abrantes FF, et al. Neurologic manifestations of antiphospholipid syndrome. Lupus 2018;27:1404-14.
8. Kim A, Chong BF. Photosensitivity in Cutaneous Lupus Erythematosus. Photodermatol Photoimmunol Photomed 2013;29:4-11.
9. Kuhn A, Herrmann M, Kleber S, et al. Accumulation of apoptotic cells in the epidermis of patients with cutaneous lupus erythematosus after ultraviolet irradiation. Arthritis Rheum 2006;54:939-50.
10. Provenzale JM, Barboriak DP, Allen NB, et al. Patients with antiphospholipid antibodies: CT and MR findings of the brain. AJR Am J Roentgenol 1996;167:1573-8.

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LETTER TO THE EDITOR

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Joint preserving surgery for osteoarthritis of the big toe using a cartilage-like implant

Dear Editor,

Osteoarthritis of the big toe (hallux rigidus) is a common arthritic condition of the first metatarsophalangeal joint (MTPJ), beginning with stiffness, pain and inflammation. This subsequently progresses to restriction of movements especially dorsiflexion.[1] Articular surface degeneration and formation of periarticular osteophytes may be seen on radiographs.[2] Common causes include activity-related repetitive trauma (sports and occupational) and inappropriate footwear.[1,3] Other factors are direct toe injury, fractures, rheumatoid arthritis, increased age, long proximal phalanx of toe, hypermobile first ray, tarsal coalition, ankylosis of sesamoids to the first metatarsal head, irregular morphology, soft tissue contracture and family history.

Treatment options of hallux rigidus remain controversial. These vary from cheilectomy, soft tissue release, first metatarsal osteotomies, arthrodesis, excisional arthroplasty; to hemiarthroplasty and total arthroplasty using different implants such as metal alloy, silastic and ceramic.[4-6] In our local practice, the commonest surgery for advanced hallux rigidus is arthrodesis. This often results in lower patient satisfaction levels owing to reduction in range of toe movement. Cartiva synthetic cartilage implant (SCI) has been approved by the US Food and Drug Administration (FDA) as an implant for hallux rigidus surgery. The polymer-based polyvinyl alcohol (PVA) implant is recognised as the first synthetic material closest to human joint cartilage. This paper discusses operative technique and clinical outcomes of this innovative joint preservation surgery.

Design and specification of implant. Cartiva SCI is a moulded cylindrical implant composed of PVA and saline. Rigorous biomechanical testing has demonstrated its ability to withstand forces normally subjected on the great toe.[7,8] Approved by the FDA in 2016 as a PVA hydrogel implant, it is currently used in the US, UK and Europe.

Indications for use. The procedure is reserved for Grade 3 and 4 hallux rigidus where the disease process would be considered moderately severe to severe.[9] Patients would have undergone a trial period of non-operative management including analgesia as well as footwear and lifestyle modification. Although this procedure is not considered first line treatment, should patients have had longstanding history of first MTPJ pain lasting several years, then it may be offered at first consultation.

Contraindications. The use of Cartiva SCI is not recommended in cases involving active infection, known/suspected allergy to PVA, gout or rheumatoid arthritis involving first MTPJ and tumour of surrounding bone or tissue.[8]

We present our series of the first 5 cases using this implant. All patients have Grade 3 or 4 hallux rigidus having failed conservative treatment. Pain, function and alignment was graded using an American Orthopaedic Foot and Ankle Society score.[10]

Operative procedure. Surgery is performed with the use of a tourniquet and prophylactic antibiotics. Approach is via a longitudinal dorsal centred over the first MTPJ, followed by dissection down to the joint capsule. The joint is exposed and the periarticular osteophytes are removed. Exposure of the metatarsal head and proximal phalanx is achieved with deep flexion of the joint. A guide wire is inserted into the medullary canal through the centre of the metatarsal head and its position is confirmed with intraoperative imaging. A cannulated drill is then used to core out of the metatarsal head to the desired size (Fig. 1A) for the Cartiva implant. Following the removal of any debris and washing out of the cavity, the implant is carefully inserted using an introducer. The press-fitted final position allows the implant to sit and a 2mm protrusion of the top of the implant into the joint is deemed the appropriate height (Fig. 1B). Range of motion of the joint and stability of implant is checked before closing the capsule.

Postoperative care. All patients were discharged on the same day of surgery. Patients were provided an orthopaedic stiff-soled sandal and allowed to weight bear on the operated foot. Early range of motion exercises were started immediately after surgery to prevent joint stiffness. Wound inspection was performed 1 week post-surgery and sutures removed after 2 weeks.

Discussion. Recent local studies of osteoarthritis in larger joints have shown that joint replacement has yielded promising results across different ethnic groups,

Table 1. Patient biodata

Case no.	Age, Sex	X-ray findings	Preoperative ROM	Postoperative ROM	Implant size (mm)	Follow-up (months)	Preoperative VAS	Postoperative VAS	Preoperative AOFAS forefoot score	Postoperative AOFAS forefoot score
1	49, Male	Arthritis, narrow joint space, lateral osteophytes	Ext: 10 Flex: 20	Ext: 70 Flex: 60	8	20	4	1	52	85
2	61, Male	Arthritis, articular cartilage defect	Ext: 5 Flex: 5	Ext: 55 Flex: 45	10	17	5	0	52	100
3	53, Female	Joint spaces reduction with eburnation of 90% of the articular surface of 1st metatarsal, and 60% eburnation of articular surface phalanx	Ext:10 Flex: 10	Ext: 60 Flex: 45	10	7	6	2	23	87
4	62, Male	Arthritis, joint space reduction, osteophytes	Ext: 20 Flex: 10	Ext: 80 Flex: 40	10	5	4	1	18	85
5	64, Female	Arthritis, joint space reduction, osteophytes	Ext: 5 Flex: 5	Ext: 50 Flex: 60	8	1	5	1	47	85

AOFAS: American Orthopaedic Foot and Ankle Society; Ext: extension; Flex: flexion; ROM: range of motion; VAS: visual analogue scale
Note: Cases 1 to 3 are Caucasians. Case 4 is a Singaporean Malay. Case 5 is a Singaporean Chinese.

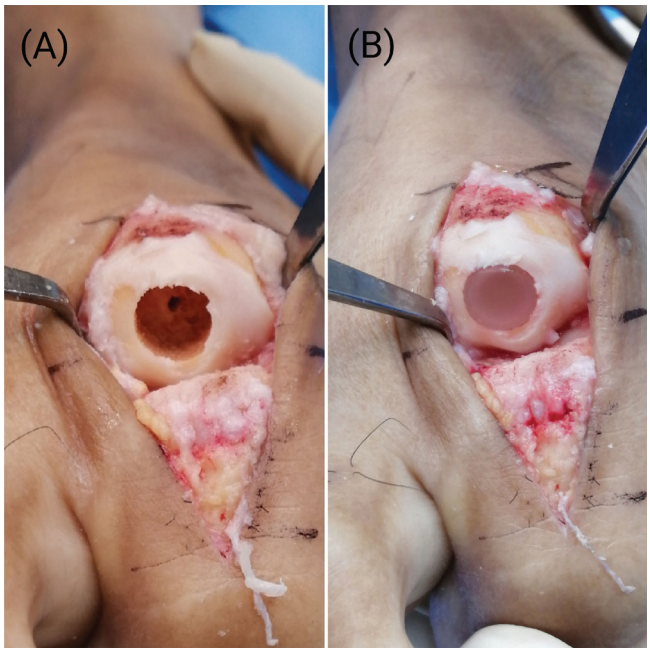

Fig. 1. Intraoperative images of operative procedure. (A) Metatarsal head following excision of surrounding osteophytes and canal preparation. Note the area of cartilage loss. (B) Well-fitted and appropriately sized (10mm diameter) Cartiva implant.

and hence patient satisfaction can be expected.[11,12] The first MTPJ is also a major site of osteoarthritis that can be treated successfully with joint replacement surgery.[1,9,11] Our paper highlights good patient satisfaction from different ethnic backgrounds (Table 1), in accordance with the local studies.[11,12]

Treatment modalities for the hallux rigidus are controversial and many options have been described in management of the disease. Non-surgical management of stage 1 and stage 2 hallux rigidus may provide some relief to the patients.[9] For advanced stage, surgical intervention is needed to reduce pain and improve functional stability. The type of surgery depends upon the stage of hallux rigidus.[13] Cheilectomy surgical procedure (removal of osteophytes and joint debridement) is usually advocated to treat mild hallux rigidus.[1] Closing wedge osteotomy (dorsal) can be performed for the phalanx to improve functional stability.[14] Arthrodesis, accepted as the gold standard technique for grade 3 and 4 hallux rigidus, provides pain relief but sacrifices joint movements.[4,8]

The biggest benefit of joint replacement surgery is preservation of joint movements and a shorter rehabilitation with immediate mobilisation. Although initial results of other implants were promising, they subsequently led to failure. Silastic (silicon rubber) resulted in osteolysis and inflammatory immune reaction causing bony resorption and implant loosening.[7] Metal alloy and ceramic implants failed because of relative hardness of the material versus bone, causing wear within the bony canal.[15]

We have presented promising results following surgery for hallux rigidus using this new implant. No complications were reported in our series. Serial radiological and clinical examination found no evidence of failure and implant loosening.

Studies in the UK and North America show similar results in favour of first MTPJ arthroplasty using Cartiva implant.[12]

We believe that for Singapore's population, joint replacement can be the "new gold standard" for moderate to advanced stages of hallux rigidus. This can benefit patients who are active and wish to have their toe movements preserved; and women who want to continue wearing high heels.[16]

REFERENCES

1. Shereff MJ, Baumhauer JF. Hallux rigidus and osteoarthrosis of the first metatarsophalangeal joint. J Bone Joint Surg Am 1998;80:898-908.
2. Harisboure A, Joveniaux P, Madi K, et al. The Valenti technique in the treatment of hallux rigidus. Orthop Traumatol Surg Res 2009;95:202-9.
3. Cannavò L, Costarella L, Pavone V, et al. Arthrodesis and Hemiarthroplasty: Different Techniques in the Treatment of Hallux Rigidus—Surgery and Postoperative Rehabilitation. J Funct Morphol Kinesiol 2016;1:102-8.
4. Bennett GL, Sabetta J. First metatarsalphalangeal joint arthrodesis: evaluation of plate and screw fixation. Foot Ankle Int 2009;30:752-7.
5. Brage ME, Ball ST. Surgical options for salvage of end-stage hallux rigidus. Foot Ankle Clin 2002;7:49-73.
6. Chee YH, Clement N, Ahmed I, et al. Functional outcomes following ceramic total joint replacement for hallux rigidus. Foot Ankle Surg 2011;17:8-12.
7. Ingham E, Fisher J. Biological reactions to wear debris in total joint replacement. Proc Inst Mech Eng H 2000;214:21-37
8. Baumhauer JF, Singh D, Glazebrook M. Prospective, randomized, multi-centered clinical trial assessing safety and efficacy of a synthetic cartilage implant versus first metatarsophalangeal arthrodesis in advanced hallux rigidus. Foot Ankle Int 2016;37:457-69.
9. Lam A, Chan JJ, Surace MF, et al. Hallux rigidus: How do I approach it? World J Orthop 2017;8:364-71.
10. Kitaoka HB, Alexander IJ, Adelaar RS, et al. Clinical rating system for the ankle-hindfoot, midfoot, hallux, and lesser toes. Foot Ankle Int 1994;15:349-53.
11. Shah NZ, Malhotra R, Hong CC, et al. Ethnic Differences in Preoperative Patient Characteristics and Postoperative Functional Outcomes after Total Knee Arthroplasty among Chinese, Malays and Indians. Ann Acad Med Singap 2018;47:201-5.
12. Huang Y, Lee M, Chong HC, et al. Reasons and Factors Behind Post-Total Knee Arthroplasty Dissatisfaction in an Asian Population. Ann Acad Med Singap 2017;46:303-9.

13. Coughlin MJ, Shurnas PS. Hallux rigidus. Grading and long-term results of operative treatment. J Bone Joint Surg Am 2003; 85:2072-88.
14. O'Malley MJ, Basran HS, Gu Y, et al. Treatment of advanced stages of hallux rigidus with cheilectomy and phalangeal osteotomy. J Bone Joint Surg Am 2013;95:606-10.
15. Cracchiolo A, Weltmer JB, Lian G, et al. Arthroplasty of the first metatarsophalangeal joint with a double-stem silicone implant. Results in patients who have degenerative joint disease failure of previous operations, or rheumatoid arthritis. J Bone Joint Surg Am 1992;74:552-63.
16. Baker MI, Walsh SP, Schwartz Z, et al. A review of polyvinyl alcohol and its uses in cartilage and orthopaedic applications. J Biomed Mater Res B Appl Biomater 2012;100:1451-7.

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LETTER TO THE EDITOR

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Improving medical adherence and antithrombotic management for patients with chronic limb threatening ischaemia in Singapore

Dear Editor,

Chronic limb threatening ischaemia (CLTI) represents the most advanced stage of peripheral artery disease (PAD), which, if left untreated, can progress to ulceration, gangrene, sepsis, major lower extremity amputation (LEA) and premature death. The prevalence of PAD ranges from 3% to 10% in the general population, increasing to 15–20% in people aged ≥70 years. According to the 2015 report by the Organization for Economic Co-operation and Development,[1] major LEA rates in Singapore are 2–3 times higher than those in Western countries, and are in fact the highest in the world. In Singapore, PAD patients are predominantly diabetic compared to PAD patients in Western populations (diabetes mellitus type 2, 90% versus 50%), younger at onset (50 vs 60 years), present with minimal claudication symptoms, and largely below-knee atherosclerotic occlusions (vs aorto-iliac-femoral disease), and more likely to have chronic renal failure (50% vs 27%).[2]

The 1-year risk of major LEA in patients with CLTI exceeds 15–20% and the 5-year all-cause mortality rate is approximately 50%.[3] As they have significant systemic atherosclerosis, patients with CLTI are at increased risk of premature death and have a higher incidence of cardiovascular (CV) events.[4] Therefore, with a heightened risk of global atherothrombosis, systemic vascular prevention strategies are essential for the best holistic treatment. Current guidelines recommend antiplatelet monotherapy for prevention of CV events with a class IA recommendation for aspirin or clopidogrel, based on results of large CV outcome trials. In contrast, dual antiplatelet therapy combining aspirin and clopidogrel is used after intervention—regardless of surgical or endovascular revascularisation for the reduction of post-procedural complications. It was given a class IIa, level C recommendation in the absence of any randomised data to support this indication.[5] A recent rapid review in the *Annals* by our group suggested adherence to evidence-based medical treatment is extremely variable and that undertreatment is common in the PAD setting.[6] Furthermore, data from Asian countries on this front are lacking.

Our institution, the Singapore General Hospital, a tertiary vascular centre that performs over 900 lower limb endovascular revascularisation procedures annually, currently sends its lower limb angioplasty data to the US Vascular Quality Initiative (VQI)[7] database and is the only participating centre from the Asia-Pacific region. Our aim is to improve the quality of our lower limb angioplasty outcomes by collating our data to allow valid comparison and benchmarking to other global centres of excellence. VQI is a network of vascular specialists seeking to improve the quality and safety of vascular care by sharing data. Consent to collect, analyse and publish anonymised patient data was waived. Since subscribing in July 2019, we have logged 1,361 procedures (1,016 limbs, 873 patients and 2,749 lesions) as of May 2021. Table 1 shows the baseline demographics, which is notably significant.

Only 73% of patients were on an antiplatelet agent (APA) and 84% on lipid lowering therapy at presentation. Furthermore, considering that approximately 40% of patients had prior peripheral vascular intervention, only 51/345 (15%) were on dual APA therapy. Potentially adjunct medical therapy plays an important role in minimising further limb and CV adverse events in what is a relentlessly progressive disease. In spite of this, best medical therapy is either being stopped or discontinued by the physician or patient at the primary and secondary level of outpatient specialist care. Valid reasons for non-adherence or discontinuation of these medications include symptoms such as muscle cramps or liver function derangement with statins, or bleeding complications and gastrointestinal upset with APA. Also, polypharmacy and altered physiological reserve increase the risk of adverse drug events in these frail and challenging patients. These latest Singapore data suggest we could do more to maximise adherence to existing PAD guidelines by trying to understand initially why a significant portion of our patients discontinue or are not put on best medical therapy.

It is also important to highlight that there may be a significant benefit for patients with PAD—both primarily and after revascularisation—in taking a combination of aspirin and low-dose rivaroxaban (rivaroxaban, a factor Xa inhibitor) to reduce first and subsequent adverse CV outcomes. There is emerging evidence that there is a fourfold risk of acute limb ischaemia and approximately 30% increased risk of

Table 1. Patient demographics

	Number of patients (n=873)	Percentage (%)
Mean age ± SD, years	69.0±10.8	
Mean BMI ± SD, kg/m^2	24.6±4.6	
Sex		
Male	566	64.8
Female	307	35.2
Ethnic group		
Asian	865	99.1
Caucasian	4	0.5
Other	4	0.5
Smoking status		
Non-smoker	496	56.8
Ex-smoker	198	22.7
Smoker	179	20.5
Comorbidities		
Hypertension	811	92.9
Diabetes	732	83.8
Coronary artery disease	512	58.6
Chronic kidney disease	303	34.7
Cerebrovascular disease	227	26.0
Dysrhythmia	160	18.3
Congestive heart failure	161	18.4
Chronic obstructive pulmonary disease	27	3.1
Medication history		
Statin	736	84.3
Antiplatelets	636	72.9
ARB	396	45.4
Anticoagulants[a]	53	6.1
Insulin	344	39.4
Non-insulin medication	388	44.4
Ambulation		
Ambulatory	406	46.5
Ambulatory with assistance	301	34.5
Wheelchair-bound	157	18.0
Bedridden	9	1.0

Table 1. Patient demographics (Cont'd)

	Number of patients (n=873)	Percentage (%)
Prior interventions		
Leg arterial bypass/ endarterectomy/PVI	345	39.5
Percutaneous coronary intervention	221	25.3
Coronary artery bypass graft	169	19.4
	Number of limbs (n=1016)	Percentage (%)
Urgency		
Emergency	598	58.9
Elective	418	41.1

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; PVI: peripheral vascular intervention; SD: standard deviation

[a] Comprising all types of anticoagulants including rivaroxaban

myocardial infarction in patients who have previously undergone a lower extremity revascularisation procedure.[8] Therefore, the need for peripheral revascularisation identifies a PAD subpopulation to be at a heightened risk of future vascular ischaemic events. The Vascular Outcomes studY of ASA (acetylsalicylic acid) alonG with rivaroxaban in Endovascular or surgical limb Revascularisation for Peripheral Artery Disease (VOYAGER PAD) study was initiated to evaluate the efficacy and safety of low dose rivaroxaban (2.5mg PO BD) used together with aspirin in high-risk PAD patients undergoing lower extremity revascularisation.[9]

This landmark study enrolled 6,564 patients in 34 countries who had PAD and had undergone lower extremity revascularisation. Patients were randomly assigned to receive either rivaroxaban or a placebo, in addition to daily aspirin. There was a 15% significant relative risk reduction of developing a first major adverse limb or CV event in patients who received rivaroxaban compared to those who received placebo, seen as early as at 3 months, with a continued effect through to 3 years follow-up. Rates of the principal safety outcome of major bleeding increased but were not significantly different between the 2 groups (2.7% vs 1.9%; P=0.07). During 3 years of follow-up, approximately a third of patients had a CV event, in spite of high utilisation of background medical therapy.[10]

However, there was an absolute risk reduction of 12.5% in those receiving low dose rivaroxaban, which

is a big advantage in avoiding the need for patients to be admitted for treatment of vascular complication. From our VQI database to date, only 17/873 (1.9%) were placed on the low dose rivaroxaban regimen following revascularisation. Cost and access to the low dose formulation may be limiting factors currently, but snapshots from the current data suggest we could do more to improve not only medical adherence to traditional APA therapy, but also start a low dose thrombin inhibitor to prevent future CV events and reduce the number of major LEAs.

REFERENCES

1. OECD. Cardiovascular Disease and Diabetes: Policies for Better Health and Quality of Care. OECD Health Policy Studies. Paris: OECD Publishing; 2015.
2. Tay WL, Chong TT, Chan SL, et al. Two-year clinical outcomes following lower limb endovascular revascularisation for chronic limb threatening ischaemia at a tertiary Asian vascular centre in Singapore. Singapore Med J 2020:1-25.
3. Duff S, Mafilios MS, Bhounsule P, et al. The burden of critical limb ischemia: a review of recent literature. Vasc Health Risk Manag 2019;15:187-208.
4. Davies MG. Criticial limb ischemia: epidemiology. Methodist DeBakey Cardiovasc J 2012;8:10-4.
5. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018;39:763-816.
6. Chan SL, Rajesh R, Tang TY. Evidence-based medical treatment of peripheral arterial disease: A rapid review. Ann Acad Med Singap 2021;50:411-24.
7. Society for Vascular Surgery. Patient Safety Organization, Vascular Quality Initiative. Available at: https://vascular.org/research-quality/vascular-quality-initiative/patient-safety-organization. Accessed on 9 April 2020.
8. Bonaca MP, Gutierrez JA, Creager MA, et al. Acute Limb Ischemia and Outcomes With Vorapaxar in Patients With Peripheral Artery Disease: Results From the Trial to Assess the Effects of V orapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis in Myocardial Infarction 50 (TRA2 degrees P-TIMI 50). Circulation 2016;133:997-1005.
9. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. N Engl J Med 2020;382:1994-2004.
10. Bauersachs RM, Szarek M, Brodmann M, et al. Total Ischemic Event Reduction with Rivaroxaban after Peripheral Arterial Revascularization in the VOYAGER PAD Trial. J Am Coll Cardiol 2021;78:317-26.

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Bone in the breast: Clinical, radiological and pathological correlation

An 84-year-old woman presented with a left breast mass that had been rapidly growing over a few months. On clinical examination, there was a large and firm left breast mass with no overlying skin change. The right breast was normal. The patient was treated in accordance with the Declaration of Helsinki, and Institutional Review Board approval was obtained.

The patient was evaluated with mammography (Fig. 1) and ultrasound scan of the left breast (Fig. 2).

Which is the most likely diagnosis?

A. Invasive ductal carcinoma
B. Invasive medullary carcinoma
C. Involuting giant fibroadenoma
D. Phyllodes tumour with heterologous osteoid component
E. Fat necrosis

Findings and diagnosis. Mammography showed a large, dense, left breast mass with lobulated, circumscribed margins. It contained a cluster of almost bone-like coarse calcifications (Fig. 1). Sonography demonstrated a 13cm, lobulated, complex solid cystic mass at the left 10 to 3 o'clock position with ill-defined margins (Fig. 2).

No axillary or distant metastases were detected on staging computed tomography.

Ultrasound-guided core needle biopsy through the solid component was performed. Microscopic examination revealed leaf-like stromal fronds with a spindle cell proliferation suggestive of a phyllodes tumour (PT) (Fig. 3). There was microscopic ossification, but no abnormal stromal cells with significant atypia were seen associated with the bone, thus favouring a benign osseous metaplastic process. Excision was advised to exclude underlying malignancy of the phyllodes tumour. In view of its large size and risk of inadequate margins, the patient underwent a mastectomy.

Pathology of the mastectomy specimen showed a malignant PT with a heterologous osteosarcomatous component (Fig. 4).

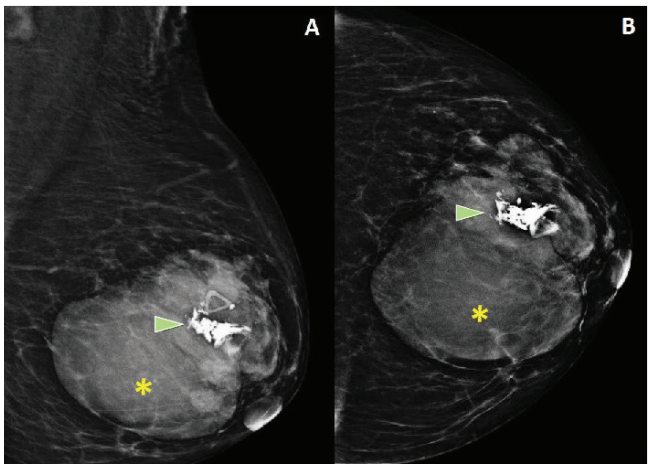

Fig. 1. Mammogram of the left breast (A) mediolateral oblique and (B) craniocaudal views show a lobulated mass (asterisks) occupying most of the breast. No spiculations are seen. The mass contains a prominent cluster of almost bone-like coarse calcifications, which appear very thick, haphazard in pattern and sharply angulated (arrowheads).

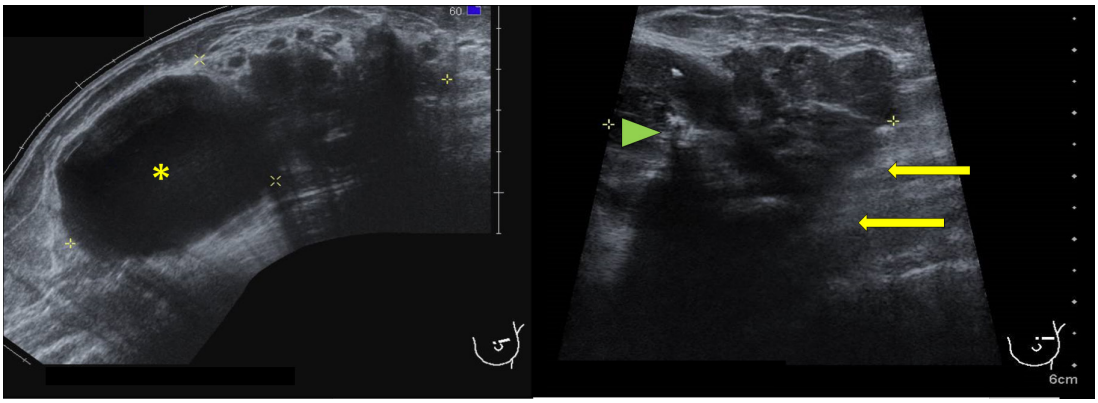

Fig. 2. Ultrasound of the left breast shows a 13cm solid-cystic mass. There is an eccentrically located cystic component with circumscribed margins (asterisk), and an adjacent lobulated hypoechoic solid component with partially indistinct margins and posterior acoustic shadowing (long arrows). Internal echogenic foci with posterior acoustic shadowing (arrow head) correspond with the coarse calcifications on mammography.

Answer: D

Discussion. In an elderly patient presenting with a rapidly enlarging breast mass, the important diagnostic differential considerations will be phyllodes tumour, primary breast sarcomas, medullary carcinomas and any type of high-grade invasive cancers.

The majority of invasive ductal carcinomas (IDCs) present as a mass with spiculated margins, which was not a feature in this case. IDC masses may contain calcifications, which are often associated with a ductal carcinoma in situ (DCIS) component. The calcifications of DCIS are usually pleomorphic or linear branching type in morphology and are <0.5mm in size.[1] These coarse calcifications seen in this case are not typical for IDC.

Medullary carcinomas are known to be rapidly growing and can present as circumscribed lobulated masses. However, they are not typically associated with calcifications, hence this diagnosis is unlikely.[1]

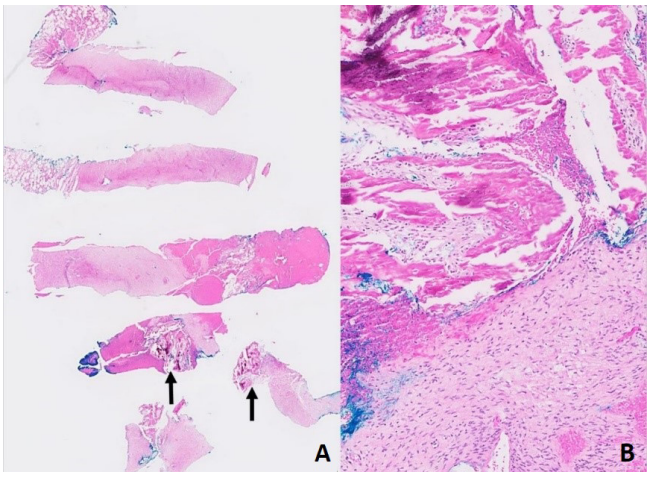

Fig. 3. (A) Core needle biopsy of the breast mass shows a spindle cell lesion with areas of ossification (arrows). (B) High magnification of the ossified portion shows association with spindle cells with relatively bland cytologic features.

Fat necrosis, which is typically associated with trauma or intervention, has a variable imaging appearance. It can develop as an irregular, spiculated mass or demonstrate clustered microcalcifications, and overlap with the imaging appearance of malignancy. However, the mass usually contains fatty radiolucent areas, and the calcifications are characteristically peripheral at the rim. Its sonographic appearance is non-specific. It can appear as an anechoic cyst, solid mass or a complex solid-cystic lesion, and should be correlated with the mammogram findings.[2] In this case, the dense solid component lack fatty radiolucent elements and the calcifications are unlike those associated with fat necrosis, which are usually dystrophic or rimmed in appearance with lucent centres.

Fibroadenomas and PT are both fibroepithelial lesions, and have overlapping radiological and histological features. However, giant fibroadenomas ≥5cm in size are seen in younger premenopausal women and do not grow after menopause. On imaging, fibroadenomas tend to be smaller (<4cm) and are usually wider than tall in orientation. Both lesions can have lobulated margins but PT tends to have bulging borders.[3] Involuting fibroadenomas can also demonstrate coarse, popcorn-like calcifications that are >2mm in size. These calcifications typically show smooth margins, unlike the irregular and angulated margins seen in this case. Intra-tumoural cystic components are usually due to clefts between the bulging nodular protuberances, and are more commonly seen in PT compared to fibroadenomas. Cystic infarctions in rapidly growing fibroadenomas and PT may also give rise to cystic areas.[3]

PTs are rare fibroepithelial neoplasms that account for <1% of all breast neoplasms, usually affecting women 40–50 years of age.[4] Based on the histological characteristics, which include nature of the tumour

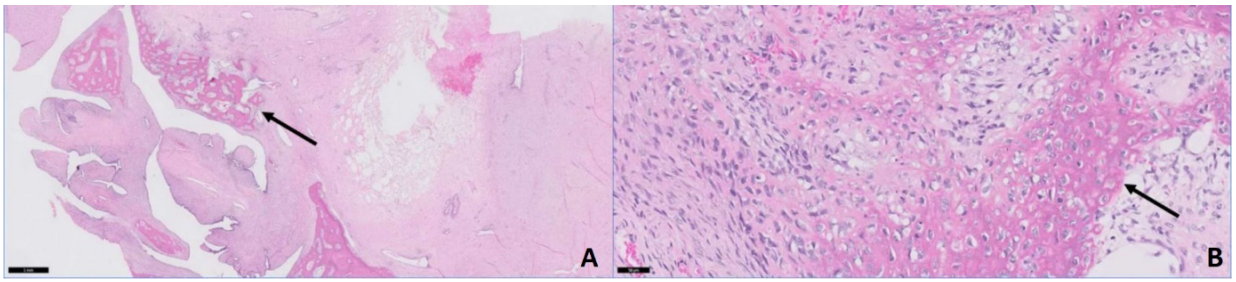

Fig. 4. (A) Histopathology of the tumour in the resected mastectomy specimen at low magnification shows characteristic stromal fronds from the phyllodes tumour. It contains haphazard bony trabeculae (arrow), which correspond with the calcific pattern seen on mammography. (B) High magnification shows anastomosing pink osteoid (arrow) among abnormal cells with discernible mitoses, consistent with malignant osteoid production in osteosarcoma.

borders, degree of stromal cellularity, stromal overgrowth, cellular atypia and the number of mitoses per 10 high power fields, they are classified into benign, borderline and malignant categories.

A study found that phyllodes tumour cells have properties of mesenchymal stem cells.[5] As malignant phyllodes tumours can have heterologous differentiation along various mesenchymal lineages (bone, cartilage, fat, muscle, etc.), the authors hypothesised that phyllodes tumour cells have mesenchymal stem cell properties and indeed, some similarities were found.[5] This ability to differentiate into various mesenchymal lineages and in this case, transform into an osteosarcomatous component with bone formation is a known feature of malignant phyllodes tumours.

PT commonly presents as a large, rapidly growing mass. Features of a regular shape with generally circumscribed margins that lack spiculations help differentiate it from other invasive breast malignancies.[6] The margins of PT also tend to be bulging and lobulated due to stromal protuberances.[6] Ill-defined margins and intra-tumoural cystic spaces, as demonstrated in this case, favour malignancy. Although coarse calcifications have been reported in PT, they are rare due to rapid tumour growth.[7]

Coarse calcifications may be seen in an involuting fibroadenoma—the calcifications of calcified fibroadenomata are typically smoothly marginated and popcorn-like.[8] This is different from the coarse calcifications in this case, which had angulated margins.

Other imaging differentials include primary breast sarcomas and metaplastic breast carcinoma. Primary breast sarcomas are a heterogeneous group of mesenchymal tumours without epithelial components, which include angiosarcoma, osteogenic sarcoma, fibrosarcoma, liposarcoma and malignant fibrous histiocytoma.[9] Metaplastic carcinoma is an invasive carcinoma with mesenchymal and epithelial components, and shows coexistence of matrix-producing, spindle cell, sarcomatous or squamous differentiations. Both types of tumours can present as a large rapidly growing mass of regular shape with circumscribed, lobulated margins.[10-12] They may appear as solid-cystic masses on sonography,[10,13] and may have coarse calcifications if there is osseous heterologous differentiation, similar to the case presented. Metaplastic breast carcinomas tend to be associated with stromal distortion.[14] Both types of tumours are rare, accounting for <1% of all breast cancers; phyllodes tumours are relatively more common in comparison.

On microscopy, malignant osteoid formation can be mistaken as collagen, especially when the osteoid is not calcified. Also, if histological ossification is not accompanied by malignant cells, interpretation as a benign metaplastic process is likely. There may be undersampling with core needle biopsies, further contributing to the challenges of accurate recognition. Knowledge of the radiological features can help alert the pathologist to the possible malignant nature of the tumour. Presurgical diagnosis of a malignant PT will be useful for surgical planning, especially if a wide local excision is planned. Surgery should aim to achieve negative margins for malignant PT to reduce the risk of local recurrence. Wide local excision with 10mm margins, without axillary staging, is the current recommended treatment according to the recent US National Cancer Comprehensive Network guidelines.[15]

REFERENCES

1. Berg WA, Birdwell RL, Gombos E, et al. Diagnostic Imaging: Breast. 1st Ed. Salt Lake City: Amirsys; 2006.
2. Taboada JL, Stephens TW, Krishnamurthy S, et al. The many faces of fat necrosis in the breast. AJR Am J Roentgenol 2009; 192:815-25.
3. Gatta G, Iaselli F, Parlato V, et al. Differential diagnosis between fibroadenoma, giant fibroadenoma and phyllodes tumour: sonographic features and core needle biopsy. Radiol Med 2011; 116:905-18.
4. WHO Classification of Tumours. Breast tumours. WHO classification of tumours series, 5th Ed, Vol 2. Lyon (France): International Agency for Research on Cancer; 2019.
5. Lin JJ, Huang CS, Yu J, et al. Malignant phyllodes tumors display mesenchymal stem cell features and aldehyde dehydrogenase/ disialoganglioside identify their tumor stem cells. Breast Cancer Res 2014;16:R29.
6. Liberman L, Bonaccio E, Hamele-Bena D, et al. Benign and malignant phyllodes tumors: Mammographic and sonographic findings. Radiology 1996;198:121-4.
7. Chao TC, Lo YF, Chen SC, et al. Sonographic features of phyllodes tumors of the breast. Ultrasound Obstet Gynecol 2002;20:64-71.
8. Bennett DL, Merenda G, Schnepp S, et al. Primary breast osteosarcoma mimicking calcified fibroadenoma on screening digital breast tomosynthesis mammogram. Radiol Case Reports 2017;12:648-52.
9. Matsumoto RAEK, Hsieh SJK, Chala LF, et al. Sarcomas of the breast: Findings on mammography, ultrasound and magnetic resonance imaging. Radiol Bras 2018;51:401-6.

10. Smith TB, Gilcrease MZ, Santiago L, et al. Imaging features of primary breast sarcoma. AJR Am J Roentgenol 2012;198:W386-93.
11. Dekkers IA, Cleven A, Lamb HJ, et al. Primary osteosarcoma of the breast. Radiographics 2019;39:626-9.
12. Yang WT, Hennessy B, Broglio K, et al. Imaging differences in metaplastic and invasive ductal carcinomas of the breast. AJR Am J Roentgenol 2007;189:1288-93.
13. Günhan-Bilgen Isil, Memiş A, Ustün EE, et al. Metaplastic carcinoma of the breast: Clinical, mammographic and sonographic findings with histopathologic correlation. AJR Am J Roentgenol 2002;178:1421-5.
14. Park JM, Han BK, Moon WK, et al. Metaplastic carcinoma of the breast: Mammographic and sonographic findings. J Clin Ultrasound 2000;28:179-86.
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast cancer (Version 5.2020).

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Rapidly progressive ulcer in an older woman

A fit and well 78-year-old woman with no significant past medical history presented to the Emergency Department with large painless perianal ulcers. It started as an erythematous patch that developed into pruritic perianal blisters, and rapidly evolved into a necrotic ulcer over 2 days. She denied any prior injury or new contacts and was not on any new medications. At presentation, she was afebrile and physical examination findings were unremarkable except for the large 16x15cm gangrenous ulcer with a black scab surrounded by an erythematous halo on the perianal region extending to the intergluteal cleft. There was another similar ulcer on the left gluteal measuring 5x3cm (Fig. 1A). Biochemical investigations showed normal leukocyte count of 9.71×10^9/L (reference range, $3.37–10.93 \times 10^9$/L) and a C-reactive protein level of 7.1mg/L (reference range <5.0mg/L). The patient had no bacteraemia. Punch biopsy was done for histological and microbiological examination.

What is the diagnosis?

A. Necrotising fasciitis of the perineum

B. Aspergillosis-related primary cutaneous ulceration

C. Rapidly developing sacral sore

D. Ecthyma gangrenosum in immunocompetent individual

E. Mucormycosis

Histology showed fibro-adipose tissue showing almost complete necrosis, mostly bland. Multiple zones of suppuration, accompanied by fungal organisms with branching hyphae (Fig. 2). No granulomatous inflammation was seen. No malignancy was identified. Initial tissue culture grew *Aspergillus flavus* and *Candida tropicalis*. She was diagnosed with ecthyma gangrenosum.

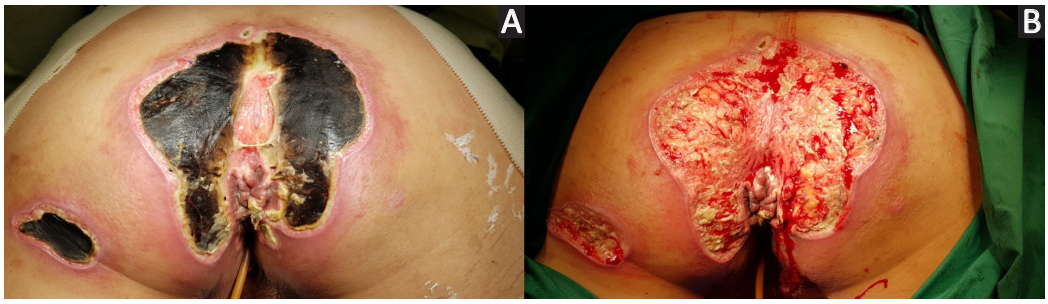

Fig. 1. Perianal necrotic ulcers prior to debridement. (A) Post debridement showing healthy adipose tissue with good vascularity, signifying a superficial process (B).

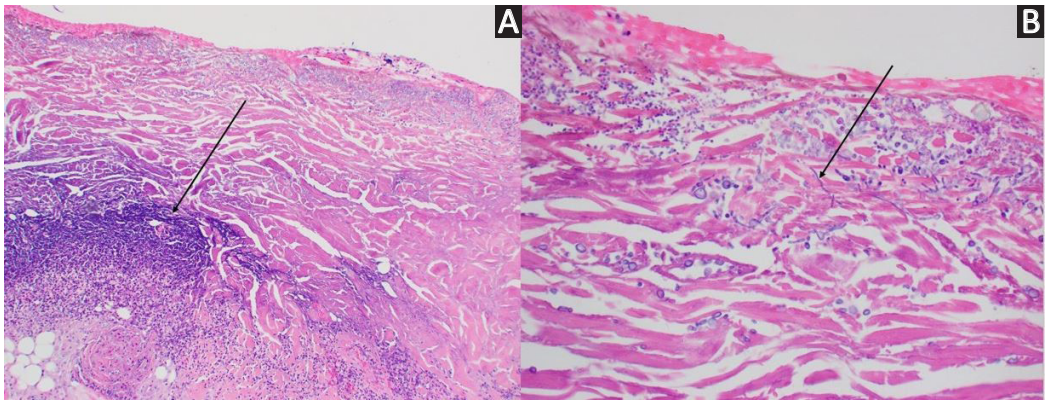

Fig. 2. (A) Histology from punch biopsy of perianal ulcers using haematoxylin and eosin stain showing suppurative necrosis at 10x magnification, and (B) with fungal elements at 40x magnification.

Answer: D

Intravenous Augmentin 1.2g TDS and oral fluconazole 100g OD were commenced. In view of the extensive skin necrosis, we performed definitive aggressive surgical debridement of the necrotic ulcers (Fig. 1B), with vacuum-assisted closure therapy applied post-excision. A rectal tube was placed for non-surgical faecal diversion. Subsequent intraoperative tissue culture grew *Pseudomonas aeruginosa*, *Escherichia coli* and *Acinetobacter baumannii*. The patient was continued on culture-directed antimicrobial treatment (IV Augmentin, oral fluconazole) for a total of 4 weeks. Her wound healed well with vacuum-assisted closure therapy after 2 months.

Although ecthyma gangrenosum usually occurs in patients who are critically ill and immunocompromised, it may develop even in the absence of bacteraemia and in immunocompetent person as illustrated in this case. Hence, ecthyma gangrenosum should be considered as a possible diagnosis even in a healthy patient especially when the ulcer is painless, rapidly progressing with characteristic central black eschar surrounded by an erythematous halo.[1-3] Primary aspergillosis resulting in ulceration with secondary bacterial infection is another likely differential as morphology and appearance of the ulceration is very similar to ecthyma gangrenosum. In this case, the rapid progression of disease and involvement of the perineum points would favour the diagnosis of ecthyma gangrenosum. Often this condition should resolve with appropriate targeted antimicrobial treatment upon diagnosis by tissue culture and microscopic examination.[1-3] However, in view of the extensive skin involvement in this case, surgical debridement of the necrotic ulcers, with vacuum-assisted closure therapy applied post-excision were done with successful outcome.

REFERENCES

1. Somer T, Finegold SM. Vasculitides associated with infections, immunization, and antimicrobial drugs. Clin Infect Dis 1995;20:1010-36.
2. Zomorrodi A, Wald ER. Ecthyma gangrenosum: considerations in a previously healthy child. Pediatr Infect Dis J 2002;21:1161-4.
3. Sarkar S, Patra AK, Mondal M. Ecthyma gangrenosum in the periorbital region in a previously healthy immunocompetent woman without bacteremia. Indian Dermatol Online J 2016;7:36-9.

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A maxillary sinus mass

A 55-year-old Chinese woman presented to the ear, nose and throat clinic with a 6-month history of left-sided blood-stained mucus. It was dark brown with no epistaxis. There was no mucopus, nasal obstruction, facial pain or fever. She denies any history of hypertension, trauma, head and neck cancer, anticoagulation use or previous irradiation. Physical examination did not reveal any external nasofacial swelling or erythema, and extraocular movement was intact. Nasoendoscopy revealed a fleshy mass with overlying blood vessels arising above the left inferior turbinate, with septal deviation towards the right (Fig. 1).

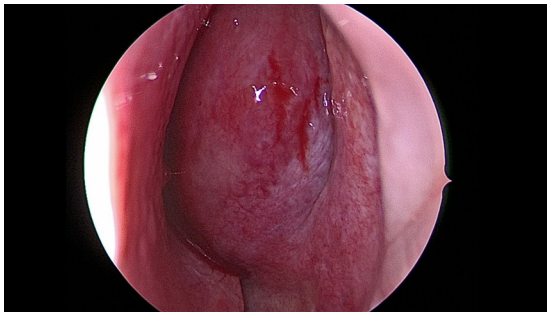

Fig. 1. Nasoendoscopic image of a nasal tumour with surface vessels.

A well-circumscribed lesion was seen in the left maxillary sinus on T2-weighted (Fig. 2) and T1-weighted magnetic resonance imaging (MRI) with contrast (Fig. 3), extending into the left nasal cavity with mass effect. The contents had serpiginous areas of marked enhancement, suggestive of areas of heterogeneous soft tissue density with interspersed blood vessels. As seen in Fig. 2, a T2-weighted MRI also depicts a hypointense peripheral rim. On computed tomography (CT) paranasal sinuses (Fig. 3), complete opacification of the left maxillary sinus is seen with medial and superior expansion with severely attenuated bony walls, particularly along the displaced left medial orbital floor and medial sinus wall, as well as a right septal deviation with no invasion into adjacent structures.

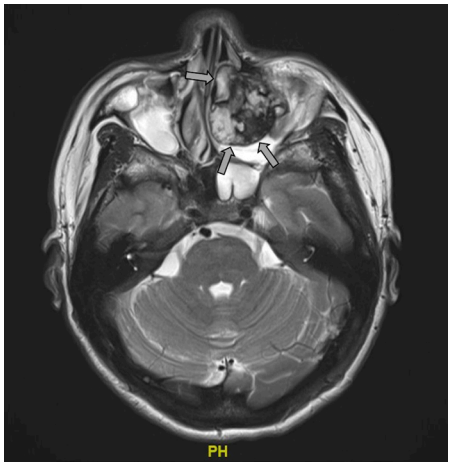

Fig. 2. Axial view of T2-weighted magnetic resonance imaging. The grey arrows illustrate a hypointense peripheral rim suggestive of a fibrous pseudocapsule.

What is the diagnosis?

A. Maxillary sinus haematoma
B. Capillary haemangioma
C. Maxillary sinus carcinoma
D. Mucocoele
E. Angiofibroma

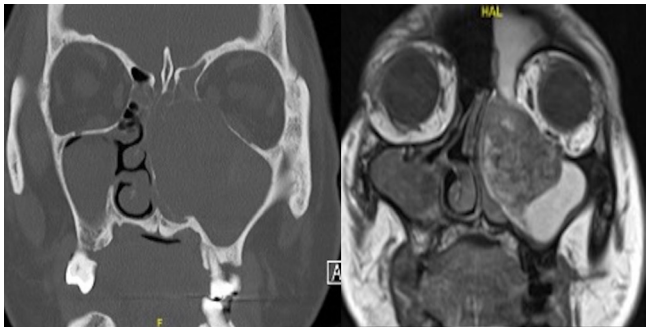

Fig. 3. Coronal views of computed tomography paranasal sinuses bone window and T1-weighted magnetic resonance imaging with contrast.

A fleshy red mass with a thin fibrous covering was seen intraoperatively. Frozen section performed revealed mainly red blood cells and acute inflammatory exudates.

Discussion. Organised haematoma of maxillary sinus (OHMS), commonly known as maxillary sinus haematoma, is a benign haemorrhagic pseudotumour. The number of reported cases is fewer than 100 cases.[1]

Ozaki et al. postulated the "Negative Spiral Theory" that illustrates how an OHMS is formed. Firstly, haemorrhage occurs in the maxillary sinus due to various causes, such as an underlying haemangioma, coagulopathy, trauma, radiation therapy, infection or inflammation. When necrosis and inflammation occurs, a fibrous capsule forms in the enclosed space, preventing the resorption of inflammatory cells and blood. Subsequently,

Answer: A

hyalinisation and angiogenesis recur. As the cycle continues, the OHMS enlarges, causing mass effect and pressure erosion on surrounding structures.[2]

The diagnosis of OHMS described by Urata et al. consists of 4 criteria: (1) findings of nasal bleeding or obstruction and a unilateral, polypoidal nasal mass; (2) CT revealing an expanding maxillary lesion with thinning or destruction of surrounding bony wall; (3) MRI showing a heterogeneous mass; and (4) histopathological findings of dilated vessels, haemorrhage and fibrin exudation.[3]

OHMS are asymptomatic when localised to the maxillary sinus. Symptoms occur when they expand, erode and displace adjacent structures. Risk factors include an underlying haemangioma, bleeding diathesis, previous trauma, radiation, infection or inflammation, hypertension or anticoagulation use. Symptoms include epistaxis, unilateral nasal congestion, cheek swelling, retroorbital pain and blurring of vision. Nasoendoscopy may show a fleshy tumour with overlying telangiectasia. Gross examination may reveal ipsilateral proptosis and hypoesthesia over the ipsilateral maxillary region.[4]

It is important to note that OHMS is not typically a top differential diagnosis in a middle-aged patient presenting with a unilateral sinonasal mass with no history of trauma or anticoagulation use.

Radiologically, OHMS has a mixture of marked heterogeneous hypo-intensity and iso-intensity on MRI, surrounded by a hypo-intense peripheral rim, which matches histologically with a fibrous pseudocapsule. These findings reflect the histological heterogeneity of the lesion, which comprises haemorrhage, fibrosis and neovascularisation.[5]

Haemangiomas can be divided into capillary or cavernous types. The former may show marked early enhancement with subsequent washout. They are described as well-circumscribed masses with no internal calcification and homogeneous enhancement.[6] Cavernous haemangiomas are usually large, inhomogeneous masses with a heterogeneous enhancement pattern of either a centripetal or multifocal nodular pattern.[7]

Sinonasal cavernous haemangiomas and OHMS can appear similar radiologically, and some believe that these entities are different manifestations of the same disease. Others are of the view that OHMS and cavernous haemangiomas are distinct entities because the vascular lumina of cavernous haemangiomas are histologically larger than those of OHMS. It is postulated that an OHMS associated with a sinonasal polyp may be a special form of angiomatous polyp, though the pathogenesis is not clearly understood.[5]

While imaging features may overlap between haemangioma, angiofibroma and OHMS, the age and sex of the patient are atypical for a haemangioma and angiofibroma. Haemangiomas are the most common head and neck tumours in children, but rarely occur in the sinonasal cavity.[6] The mass is also more anteriorly centred in the left maxillary sinus whereas an angiofibroma typically occurs around the sphenopalatine foramen, and almost always occur in young men. Enhancement in a large cavernous haemangioma or angiofibroma may be more marked than what is seen in this lesion. Mucocoeles are typically non-enhancing. Carcinoma has a solid pattern of nodular enhancement and typically shows invasive features extending into surrounding soft tissue as well as the ipsilateral ethmoid sinuses.[8]

Histopathological confirmation is required to rule out differentials. Histopathology for this patient revealed blood and fibrinous material, haemorrhagic and inflamed granulation tissue with underlying fibrosis, chronic inflammation and ectatic vessels with organising haematoma, consistent with the description of OHMS in literature.

Management of OHMS typically involves surgical resection, which is diagnostic and curative should the mass be resected completely. Bleeding diathesis must be optimised as OHMS may be haemorrhagic and cause massive bleeding. Both open and endoscopic approaches have been employed in the removal of this haematoma. Given its benign condition, most lesions are well circumscribed rather than infiltrative, and can be adequately addressed by an endoscopic middle meatal antrostomy.[9,10]

REFERENCES

1. Almasoud M, Alhumaidan A, Ashoor M. Maxillary sinus hematoma: Current pathogenesis and management. Egyptian Journal of Ear, Nose, Throat and Allied Sciences 2014;15:37-40.
2. Ozaki M, Sakai S, Ikeda H. Hemangioma of the nasal cavity and sinuses-a report of twenty five cases. Otolaryngol Head Neck Surg (Tokyo). 1977;49:8.
3. Urata S, Ohki M, Tsutsumi T, et al. Organised haematoma of the maxillary sinus: pathophysiological differences suggesting a new aetiological hypothesis. J Laryngol Otol 2013;127:519-24.
4. Tabaee A, Kacker A. Hematoma of the maxillary sinus presenting as a mass--a case report and review of literature. Int J Pediatr Otorhinolaryngol 2002;65:153-7.
5. Kim E, Kim H, Chung S, et al. Sinonasal Organized Hematoma: CT and MR Imaging Findings. Am J Neuroradiol 2008;29:1204-8.
6. Dillon W, Som P, Rosenau W. Hemangioma of the nasal vault: MR and CT features. Radiology 1991;180:761-5.

7. Kim H, Kim J, Kim J, et al. Bone erosion caused by sinonasal cavernous hemangioma: CT findings in two patients. Am J Neuroradiol 1995;16:1176-8.
8. Lee H, Smoker W, Lee B. Organized Hematoma of the Maxillary Sinus: CT Findings. Am J Roentgenol 2007;188:370-3.
9. Yokoi H, Arakawa A, Matsumoto F, et al. Organized hematoma of the maxillary sinus: a clinicopathologic study of 5 cases. Ear Nose Throat J 2014;93:23-6.
10. Imayoshi S, Kanazawa T, Fukushima N et al. Three Cases of Organized Hematoma of the Maxillary Sinus: Clinical Features and Immunohistological Studies for Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor 2 Expressions. Case Rep Otolaryngol 2015;2015:846832.

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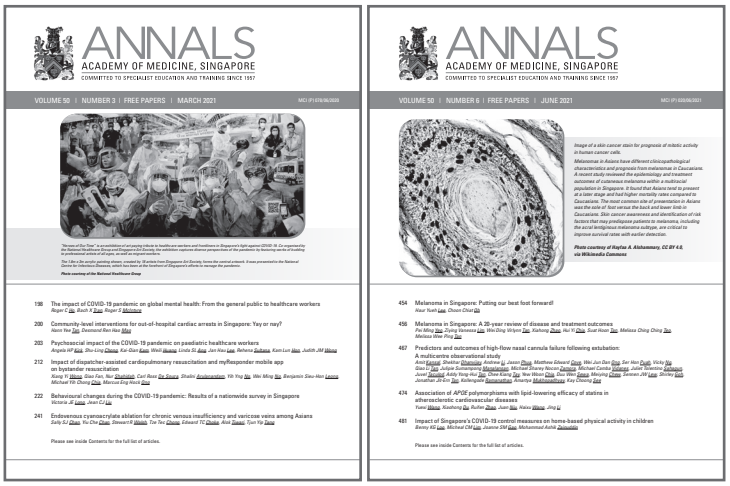

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