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"Education is the movement from darkness to light."

Allan Bloom (1930 – 1992)
American philosopher

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Editorial

The Art of Public Health in the Context of a Paradigm Shift

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Despite advancements in medical technologies, the art of medicine based on a one-to-one doctor-patient relationship has remained largely unchanged. Hippocrates, the founder of medicine, said this in the 4th century BC, "Cure sometimes, treat often, comfort always". Sir William Osler, father of modern medicine also said in the 19th century that, "The practice of medicine is an art, based on science." More recently, Harriet Hall, retired American family physician and former United States (US) Air Force flight surgeon wrote, "Medicine is not an art like painting. Neither is it a science like physics. It's an applied science." It is now generally accepted that medicine is more than just the application of scientific biomedical knowledge and skills, it is also about exhibiting good communication skills and empathy, being professional, and respecting the values and emotional feelings (including spiritual) of the patient. To the public health practitioner, the art of medicine extends beyond the one-to-one to the one-to-many setting. Charles Edward Winslow's (Professor of Public Health at Yale University from 1915 to 1945) insightful definition of public health in 1920[1]—"the science and the art of preventing disease, prolonging life, and promoting physical health and efficiency through organised community efforts"—highlights the hallmarks of public health practice. In 1985, the late Geoffrey Rose, an eminent epidemiologist, published his classic paper on "sick individuals and sick populations" which remains highly relevant to modern public health policy and practice until today.[2] High-risk individual and population approaches to improving health are fundamentally different and achieve different aims. The individual strategy focuses on reducing the disease risk factors of high-risk individuals, in contrast to the population strategy that aims to control the causes of incidence through shifting the entire distribution of a disease risk factor in the population. As public health practitioners, we must ensure that the art of our practice keeps up with the times, particularly in the context of a rapid paradigm shift.[3,4] The public health paradigm is always changing[3,4] from the challenge of improving environmental sanitation, housing conditions, food and water safety during the Industrial Revolution, to the discovery of pasteurisation and antibiotics during the 19th and 20th centuries, and to the recent threat of emerging and re-emerging infectious diseases and the increasing burden of chronic diseases in the 21st century. As public health practitioners of today, we need to learn how to assess the risks of such challenges to the population, communicate them effectively and timely as well as develop strategies to deal with them.

In the context of communicable diseases such as human immunodeficiency syndrome (HIV) and sexually transmitted infections (STIs), where development of effective vaccinations is still on-going (except for human papillomavirus), the main preventive strategy is still to minimise exposure and promote safe sexual behaviour.[5] Although educational programmes on HIV/STI prevention have shown some success through a marked increase in condom use among the brothel-based sex workers in Singapore, the challenge remains to promote consistent condom use among the other hard-to-reach population groups such as men who have sex with men, female entertainment establishment workers and intravenous drug users.[6] Dengue fever is an example of a re-emerging infectious disease that is endemic in the tropical world.[7] To the patient and the clinician, dengue fever is a clinical diagnosis. However to the public health practitioner, he or she would be more concerned with the social and economic cost to society, breaking the chain of transmission by surveillance of on-going dengue cluster, stepping up vector control interventions, and preparing the healthcare system for the potential surge in dengue cases. In the absence of an effective tetravalent vaccine for dengue fever, vector control is a crucial preventive measure,[8] meaning that we have to modify public behaviour to stop

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breeding mosquitoes.

Other than changing human behaviour, risk communication is also another important aspect of the art of public health. Effective and timely risk communication plays a vital role in mitigating the adverse impacts of a public health emergency.[9] The recent Middle East respiratory syndrome (MERS) and the severe acute respiratory syndrome (SARS) outbreak in 2003 have shown that risk communication is an art. MERS had spread fear among the public community in South Korea, as schools were closed temporarily and consumer spending dipped.[10]

The world has seen an unprecedented burden brought about by non-communicable diseases (NCDs), and changing lifestyle behaviour is increasingly at the heart of healthcare. Although tobacco use is the single most preventable cause of death,[11] tobacco use still costs the world US$200 billion and results in nearly 6 million deaths annually.[12] The tobacco epidemic continues to expand because of the addictive nature of nicotine, the on-going industry marketing and population growth in countries where tobacco use is increasing.[12] Though strong evidence of the harmful public health consequences of tobacco use have been established decades ago, we are still advocating for tobacco control today. Why is this so? There is no easy solution, as with majority of the public health challenges that are plaguing today's society. Changing lifestyle behaviour, including smoking behaviour, is more than just producing the scientific evidence. The greatest challenge lies in how we promote and sustain behavioural change among the smokers and at the same time prevent uptake of smoking among the youth in the totality of the tobacco industry and commercial market, which continues to maintain the marketability and profitability of the product despite its clear undesired public health effects.

Similarly, the rapid spread of obesity within a few generations globally indicates that we have on hand a very complex issue.[13] From a public health perspective, the aetiology of obesity is not only multifactorial, but involves complex interactions of biological, psychological, cultural, behavioural, social, economic, environmental, technological, and political factors.[14] To complicate matters, the tactics and strategies used by the food industries are extremely creative and adaptive to the changing needs of the population. The challenge continues for the public health practitioners: are we striving to develop our art to adapt to this rapidly changing paradigm?

In recent years, rapid advancements in genomic medicine have revolutionised our understanding of new approaches to prevention and therapy for chronic diseases. Genomic medicine is a potential tool to tailor the delivery of chronic disease care at the individual level by using patients' genomic information to design more effective drugs, to prescribe the best treatment for each patient as well as to identify and monitor individuals at high risk from disease.[15] Despite the promises brought about by genomic discovery, we must not forget that lifestyle behaviour still plays a major role in the development, aggravation, and perpetuation of chronic diseases.[16]

Behaviour change has become a central theme in public health practice, of which prevention has an increasing role to play in the delivery of health services at different levels. It should be clear that the public health practitioner is no longer dealing with simple systems that can be predicted and controlled, but complex adaptive systems with multiple points of equilibrium that are always interacting with one another. To perfect the art of public health practice, we must shift our mindset from that of dominion and independence to greater interdependence and collaboration. As the highest member of the biological order, we are also the most complex, not just physically, but psychologically, socially and spiritually. This is also apparent in the way we define health. The most commonly quoted definition of health is that formalised by the World Health Organization (WHO) in 1946, "a complete state of physical, mental and social well-being, and not merely the absence of disease or infirmity".[17] Given the rising chronic health problems and increasing life expectancy, critics of the WHO definition have called for a more appropriate definition. However the search for a consensus definition continues as the following questions remain to be answered: Should health be viewed as a continuum from ill health to well-being? Is well-being equivalent to non-disease? Is there a level of health that is optimal? In trying to maintain and promote the health of our people, medical care is doing a great job taking care of the sick patients. But that is not enough. The rest of the community which is not in hospital is not necessarily well.

It is long overdue that the public health practitioner must move from a disease-centric approach of health towards a more socioecological perspective as the profession continues to perfect its art. This is particularly crucial in the context of the new care model and the regional health system in Singapore where we talk about integrated care to maintain a healthy population, from preventive care to primary, secondary and tertiary care. To continue to attain the mission of keeping healthcare affordable for all in Singapore, the public health practitioner must strive to develop his or her art by promoting preventive measures through behavioural change and ensuring right-siting of care so that hospitalisations are kept to the minimal. Often, our real need is not to have more facts, but better ideas to control the problems. The task of changing human behaviour is one that requires much creativity and ingenuity.

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Original Article

2015 Young Surgeon's Award Winner: Long-term Prognosis in Patients with Diabetes Mellitus after Coronary Artery Bypass Grafting: A Propensity-Matched Study

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Abstract

Introduction: We aimed to determine the impact of diabetes mellitus (DM) on long-term survival after coronary artery bypass grafting (CABG) in patients with multivessel coronary artery disease. Materials and Methods: A retrospective review was conducted for 5720 consecutive patients who underwent isolated first CABG between 1982 and 1999. Outcomes were reviewed to include in-hospital mortality and long-term survival. Mean follow-up was 13.0 ± 5.8 years. To obtain comparable subgroups, 561 diabetic patients were matched with 561 non-diabetic controls based on estimated propensity scores. Results: Mean age was 59.3 ± 9.1 years with 4373 (76.5%) males. Amongst 5720 patients, 1977 (34.6%) had DM. Hypertension and dyslipidaemia were the most common cardiovascular comorbidities, present in 2920 (51.0%) and 2664 patients (46.6%) respectively. Emergency surgery was performed in 563 patients (9.8%). In-patient mortality occurred in 115 patients (2.0%), 48 (2.4%) in the DM group and 67 (1.8%) in the non-DM group, (*P* = 0.102). In the unmatched cohort, overall 20-year survival rates were 30.9 ± 1.6% in diabetics and 49.2 ± 1.0% in non-diabetics (*P* <0.001). Freedom from cardiac mortality at 20 years was 56.0 ± 2.0% in diabetics and 68.4 ± 1.0% in non-diabetics (*P* <0.001). In the propensity-matched group, overall 20-year survival rates were 35.4 ± 2.5% in diabetics and 48.9 ± 2.9% in non-diabetics (*P* <0.001). Freedom from cardiac mortality at 20 years was 57.8 ± 3.0% in diabetics and 70.2 ± 2.9% in non-diabetics (*P* = 0.001). Multivariable Cox regression analysis identified age (hazard ratio (HR): 1.03/year), female gender (HR: 1.43), DM (HR: 1.51), previous myocardial infarction (HR: 1.54) and left ventricular ejection fraction (LVEF) <35% (HR: 2.60) as independent factors influencing long-term cardiac mortality. Conclusion: Despite low operative mortality, long-term survival and freedom from cardiac death are significantly lower in patients with DM compared to non-diabetics. Aggressive treatment of DM, cardiovascular comorbidities and smoking cessation are essential to improve long-term survival in diabetic patients.

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Key words: Cardiac mortality, Myocardial revascularisation, Survival outcomes

Introduction

Diabetes mellitus (DM) is a major risk factor for cardiovascular disease, and coronary artery disease is the leading cause of death among adult diabetics. In Singapore, the proportion of people affected by diabetes has increased from 8.2% in 2004 to 11.3% in 2010.[1]

Coronary artery bypass grafting (CABG) is a well-accepted treatment in patients with multivessel coronary artery disease since the 1970s. The major aims of CABG are to improve the quality of life by relieving symptoms of angina and also to increase life expectancy. As coronary artery disease may continue to progress following revascularisation, CABG is ultimately a useful but palliative treatment of a progressive disease. In general, around 20% of patients undergoing CABG suffer from DM. For patients with diabetes and advanced coronary artery disease, high-level evidence has emerged showing CABG to be superior to percutaneous coronary intervention (PCI) in reducing rates of death and myocardial infarction (MI).[2] Kurlansky et al studied a propensity-matched cohort of diabetic and non-diabetic patients who underwent coronary revascularisation following non-ST-elevation myocardial infarction and reported that diabetic patients benefit from improved long-term survival and reduced major adverse cardiac events with CABG versus PCI.[3]

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Previous studies have demonstrated the adverse effect of DM on both short- and long-term survival after CABG.[4-7] This large retrospective study was conducted to determine the effect of DM on long-term survival outcomes after CABG in our local population.

Material and Methods

Following approval from the local institutional review board (reference: 2007/095/C), a retrospective case-note and database review was performed on consecutive patients who had undergone isolated first CABG at our tertiary referral centre. Surgical outcomes were reviewed to include in-hospital mortality and long-term survival. Between August 1982 and December 1999, 5720 patients underwent isolated first CABG at National Heart Centre Singapore (NHCS), of which 1977 patients (34.6%) had existing DM. Patients who underwent reoperative CABG and CABG with concomitant cardiac surgical procedures such as valve replacement, repair of ventricular septal rupture or aneurysmectomy were excluded. Both elective and urgent surgeries were included. The diagnosis of diabetes was based on a history of previously diagnosed DM or current drug therapy for DM.

To obtain comparable subgroups, a one-to-one matched analysis based on estimated propensity scores for patients with DM and non-diabetic controls yielded 2 groups comprising 561 patients each. Information regarding the cause and date of death were obtained from hospital records, supplemented by data from the National Registry of Deaths.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for Social Science, version 17 (SPSS, Chicago, IL, USA). Continuous variables were expressed as means with standard deviation and were compared using two-tailed t-test. Categorical variables, expressed as percentages, were analysed with χ^2 or Fisher's exact test. Before performing propensity score matching, we conducted a univariable analysis of potentially confounding baseline covariates associated with diabetes. A propensity score was then estimated with the use of a logistic regression model fit with the 8 factors identified—age, gender, left ventricular ejection fraction (LVEF), presence of hypertension, dyslipidaemia, end-stage renal failure, history of smoking and left internal mammary artery to left anterior descending artery (LIMA-LAD) grafting. Diabetic patients were matched in a 1:1 ratio to patients without diabetes on the basis of propensity score, following a greedy nearest neighbour matching without replacement algorithm. Each matched pair was unique, and data for unmatched patients in either group were not used in subsequent analyses. Survival function and freedom from morbid events were presented using Kaplan-Meier survival curves and comparisons performed with log-rank test. Cox multivariable regression analysis was used to identify the independent predictors of long-term outcomes. Preoperative and operative variables with a univariate P <0.10 or those judged to be clinically important were entered into the multivariable Cox model. All two-tailed P values <0.05 were taken as significant.

Surgical Technique

All operations were performed via median sternotomy using moderately hypothermic (30˚C to 32˚C) cardiopulmonary bypass (CPB) instituted with ascending aortic and dual-stage right atrial cannulation. Aortic cross-clamping and intermittent blood cardioplegia for myocardial protection was applied in all cases. CABG was performed to all major territories as long as there appeared to be viable myocardium and the coronary arteries were not too small (<1.5 mm) or too heavily calcified. Bypass conduits included the LIMA (grafted to the LAD), saphenous vein grafts and radial artery grafts from the non-dominant arm. Surgical and myocardial preservation techniques remained largely unchanged during the study period.

Results

Mean age was 59.3 ± 9.1 years with 4373 (76.5%) males. The clinical characteristics of the unmatched study groups are shown in Table 1. Hypertension and dyslipidaemia were the most common cardiovascular risk factors, being present in 2920 (51.0%) and 2664 patients (46.6%) respectively. Amongst 5720 patients, 1977 (34.6%) had existing DM; 563 patients (9.8%) underwent emergency surgery within 24 hours of hospital admission. The most common indications for emergency CABG were angina refractory to medical therapy and high-risk coronary anatomy with critical stenosis. Except for body surface area, all other preoperative and operative variables showed significant differences between the diabetic and non-diabetic patients. Results for multivariable Cox regression analysis of factors affecting long-term freedom from cardiac death in the unmatched cohort are shown in Table 2.

The preoperative and operative data of the propensity-matched pairs are shown in Table 3. The number of distal anastomoses was higher in the diabetic group than in the non-diabetic group (3.6 ± 0.9 vs 3.4 ± 1.0, P = 0.009). There was a trend towards a larger proportion of patients with a previous MI in the DM group (P = 0.064). Other variables were not significantly different between the 2 groups. Inpatient mortality occurred in 115 patients (2.0%), 48 in the DM group (2.4%) and 67 in the non-DM group (1.8%), (P = 0.102).

Table 1. Preoperative and Operative Data of 5720 Patients Undergoing First CABG

Variable	All Patients* n = 5720 (%)	Diabetic* n = 1977 (%)	Non-Diabetic* n = 3743 (%)	*P* Value
Demographics				
Age (years)	59.3 ± 9.1	60.9 ± 8.4	58.4 ± 9.3	<0.001
Gender (male)	4373 (76.5)	1327 (67.1)	3046 (81.4)	<0.001
BSA (m^2)	1.71 ± 0.17	1.71 ± 0.18	1.71 ± 0.17	0.204
BMI (kg/m^2)	23.2 ± 2.6	23.0 ± 2.5	23.3 ± 2.7	<0.001
Obesity (BMI >25 kg/m^2)	1142 (20.0)	346 (17.5)	842 (22.5)	<0.001
Comorbidities				
History of smoking	1424 (24.9)	567 (28.7)	857 (22.9)	<0.001
End-stage renal failure	134 (2.3)	67 (3.4)	67 (1.8)	<0.001
Hypertension	2920 (51.0)	1415 (71.6)	1505 (40.2)	<0.001
Hyperlipidaemia	2664 (46.6)	1186 (60.0)	1478 (39.5)	<0.001
LVEF category				
LVEF >50%	3021 (52.8)	884 (44.7)	2137 (57.1)	<0.001
LVEF 35% to 50%	2027 (35.4)	803 (40.6)	1224 (32.7)	<0.001
LVEF <35%	672 (11.8)	290 (14.7)	382 (10.2)	<0.001
Previous myocardial infarction	2532 (44.3)	1054 (53.3)	1478 (39.5)	<0.001
Left main coronary artery disease	678 (11.8)	184 (9.3)	494 (13.2)	<0.001
Emergency surgery	563 (9.8)	249 (12.6)	314 (8.4)	<0.001
Duration of cardiopulmonary bypass	73.9 ± 65.5	62.8 ± 64.5	77.8 ± 65.5	<0.001
Duration of aortic cross-clamping	41.0 ± 37.5	34.1 ± 35.1	43.5 ± 38.0	<0.001
LIMA to LAD grafting	4181 (73.1)	1542 (78.0)	2639 (70.5)	<0.001
Number of bypass grafts	3.4 ± 1.0	3.5 ± 0.9	3.4 ± 1.0	0.004

BMI: Body mass index; BSA: Body surface area; CABG: Coronary artery bypass graft; LAD: Left anterior descending artery; LIMA: Left internal mammary artery; LVEF: Left ventricular ejection fraction

*Values for continuous variables are expressed as mean ± standard deviation.

Survival data was available for all 5605 patients (98.0%) surviving to hospital discharge. The mean duration of follow-up was 13.0 ± 5.8 years (range, 0.1 to 24.7 years). During the follow-up period in the unmatched cohort, 1072 diabetic (54.2%) and 1589 non-diabetic patients (42.5%) died (*P* <0.001). Overall 20-year survival rates were 30.9 ± 1.6% in diabetics and 49.2 ± 1.0% in non-diabetics (*P* <0.001, Fig. 1A). The most common causes of non-cardiac death were malignancy (27.8%), pneumonia (18.6%) and stroke (15.7%). Death from cardiac causes occurred in 523 diabetic (26.5%) and 867 non-diabetic patients (23.2%), (*P* = 0.006). Freedom from cardiac mortality at 20 years was

Table 2. Multivariable Cox Regression Analysis for Predictors of Late Cardiac Mortality in 5720 Patients Undergoing First CABG

Variable	Hazard Ratio (HR)	95% CI	*P* Value
Age	1.022	1.015 – 1.030	<0.001
Female gender	1.162	1.003 – 1.347	0.045
Obesity	1.225	1.063 – 1.412	0.005
Diabetes mellitus	1.378	1.195 – 1.588	<0.001
End-stage renal failure	2.765	1.904 – 4.014	<0.001
History of smoking	1.183	1.022 – 1.371	0.025
LVEF 35% to 50%	1.425	1.231 – 1.650	<0.001
LVEF <35%	2.925	2.448 – 3.494	<0.001
Non-usage of LIMA-LAD graft	1.578	1.389 – 1.796	<0.001

CABG: Coronary artery bypass graft; LAD: Left anterior descending artery; LIMA: Left internal mammary artery; LVEF: Left ventricular ejection fraction

Table 3. Preoperative and Operative Data of 1122 Propensity-Matched Patients Undergoing First CABG

Variable	All Patients* n = 1122 (%)	Diabetic* n = 561 (%)	Non-Diabetic* n = 561 (%)	*P* Value
Demographics				
Age (years)	60.4 ± 7.2	60.4 ± 7.2	60.5 ± 7.3	0.885
Gender (male)	862 (76.8)	431 (76.8)	431 (76.8)	1.000
BSA (m^2)	1.72 ± 0.16	1.73 ± 0.17	1.71 ± 0.16	0.122
BMI (kg/m^2)	23.1 ± 2.4	23.2 ± 2.3	23.1 ± 2.4	0.463
Obesity (BMI >25 kg/m^2)	217 (19.3)	111 (19.7)	106 (18.9)	0.734
Comorbidities				
History of smoking	312 (27.8)	156 (27.8)	156 (27.8)	1.000
End stage renal failure	2 (0.2)	1 (0.2)	1 (0.2)	1.000
Hypertension	774 (69.0)	387 (69.0)	387 (69.0)	1.000
Hyperlipidaemia	565 (50.4)	286 (51.0)	279 (49.7)	0.676
LVEF category				
LVEF >50%	617 (55.0)	312 (55.6)	305 (54.4)	0.771
LVEF 35% to 50%	394 (35.1)	197 (35.1)	197 (35.1)	0.771
LVEF <35%	111 (9.9)	52 (9.3)	59 (10.5)	0.771
Previous myocardial infarction	557 (49.6)	294 (52.4)	263 (46.9)	0.064
Left main coronary artery disease	187 (16.7)	84 (15.0)	103 (18.4)	0.128
Emergency surgery	106 (9.5)	56 (10.0)	50 (8.9)	0.534
Duration of cardiopulmonary bypass	63.7 ± 63.2	65.2 ± 64.5	62.4 ± 62.1	0.523
Duration of aortic cross-clamping	35.0 ± 34.4	36.2 ± 34.4	34.0 ± 34.4	0.373
LIMA to LAD grafting	957 (85.3)	482 (85.9)	475 (84.7)	0.555
Number of bypass grafts	3.5 ± 1.0	3.6 ± 0.9	3.4 ± 1.0	0.009

BMI: Body mass index; BSA: Body surface area; CABG: Coronary artery bypass graft; LAD: Left anterior descending artery; LIMA: Left internal mammary artery; LVEF: Left ventricular ejection fraction

*Values for continuous variables are expressed as mean ± standard deviation.

56.0 ± 2.0% in diabetic and 68.4 ± 1.0% in non-diabetic patients (*P* <0.001) (Fig. 1B). The most common causes of cardiac death were MI (51.2%) and congestive cardiac failure (41.9%).

During the follow-up of the propensity-matched group, 310 diabetic (55.3%) and 228 non-diabetic patients (40.6%) died (*P* <0.001). Overall 20-year survival rates were 35.4 ± 2.5% in diabetics and 48.9 ± 2.9% in non-diabetics (*P* <0.001) (Fig. 2A). Death from cardiac causes occurred in 157 diabetic (28.0%) and 118 non-diabetic patients (21.0%), (*P* = 0.007). Freedom from cardiac mortality at 20 years was 57.8 ± 3.0% in diabetics and 70.2 ± 2.9% in non-diabetics (*P* = 0.001) (Fig. 2B). Fatal stroke occurred in 24 patients, 17 (3.0%) in the DM group and 7 patients (1.2%) in the non-DM group (*P* = 0.039). Multivariable Cox regression analysis (Table 4) identified age, female

Table 4. Multivariable Cox Regression Analysis for Predictors of Late Cardiac Mortality in 1122 Propensity-Matched Patients Undergoing First CABG

Variable	Hazard Ratio (HR)	95% CI	*P* Value
Age	1.025	1.006 – 1.045	0.010
Female gender	1.425	1.037 – 1.958	0.029
Diabetes mellitus	1.508	1.179 – 1.930	0.001
History of smoking	1.321	0.995 – 1.754	0.054
Previous myocardial infarction	1.542	1.170 – 2.032	0.002
LVEF <35%	2.595	1.795 – 3.753	<0.001

CABG: Coronary artery bypass graft; LVEF: Left ventricular ejection fraction

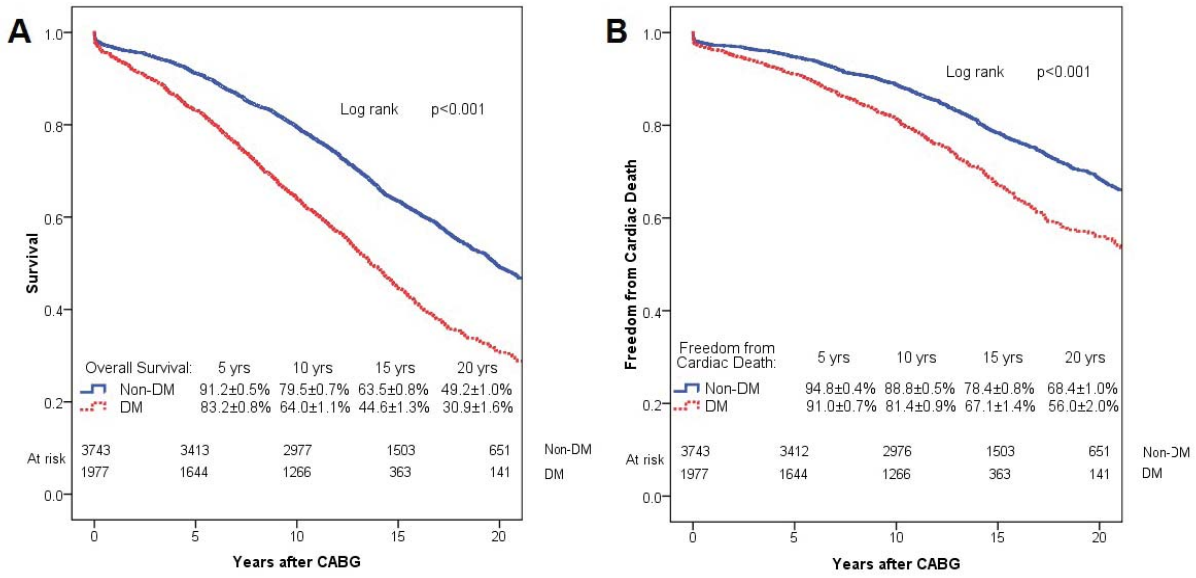

Fig. 1. Kaplan-Meier estimate of A) overall survival and B) freedom from cardiac death, in 5720 patients undergoing first CABG, including operative deaths.

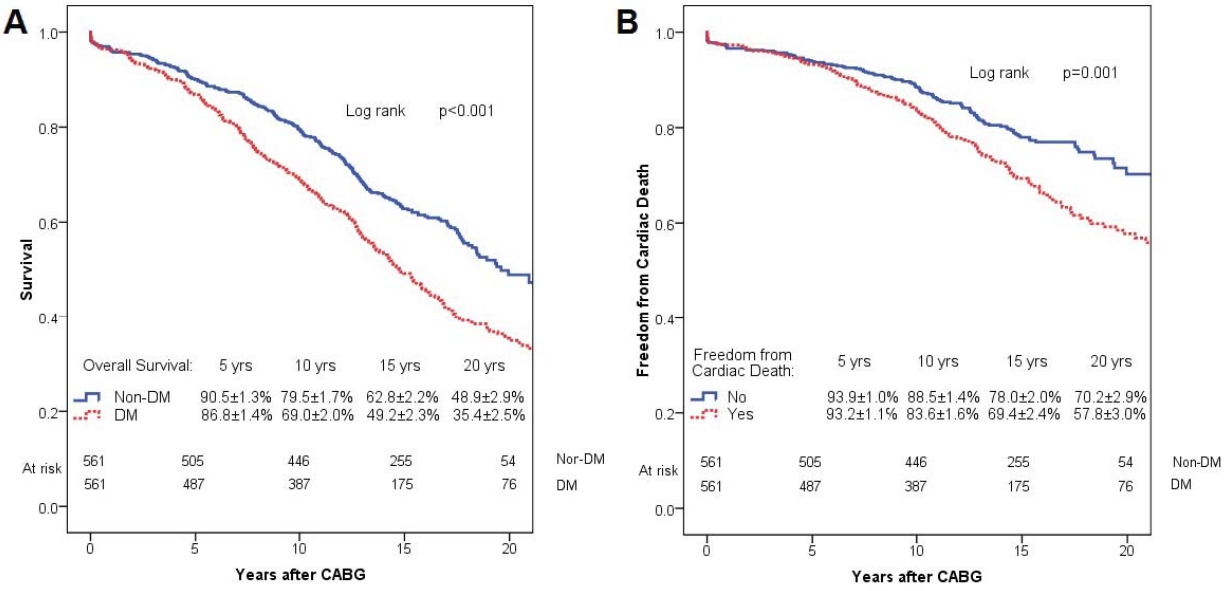

Fig. 2. Kaplan-Meier estimate of A) overall survival and B) freedom from cardiac death, in 1122 propensity-matched patients undergoing first CABG, including operative deaths.

gender, the presence of DM, previous MI and severely impaired LVEF (<35%) as factors influencing long-term freedom from cardiac death.

Discussion

As the unmatched groups in our study population had significant differences in most of the preoperative and intraoperative variables, we studied the influence of diabetes on the long-term survival outcomes after CABG by matching a large number of diabetic and non-diabetic patients according to 8 important clinical characteristics, to make the study groups as comparable as possible. After propensity-matching, apart from the number of bypass grafts received, the 2 propensity-matched groups were comparable. Although statistically significant, in the setting

of complete revascularisation of all ischaemic territories, the minor difference in the number of bypass grafts received was unlikely to be clinically significant.

In-hospital mortality after CABG was similar (2.0%) in diabetic and non-diabetic patients with multivessel coronary artery disease (2.4% in diabetics vs 1.8% in non-diabetics, $P = 0.102$). After matching with relevant clinical factors for coronary artery disease, a similar inpatient mortality rate of 2.1% was observed in the propensity-matched cohort (DM vs non-DM, $P = 1.000$). Our in-hospital mortality compares favourably to the results of a large study reported by Carson et al[5] which included 146,786 patients undergoing isolated CABG. In this study, 30-day mortality was higher in both diabetic and non-diabetic patients (3.7 and 2.7%, respectively) and diabetes was found to be an independent predictor of 30-day mortality (odds ratio (OR): 1.23). Similar to the findings by other authors,[8,9] in-hospital mortality was not significantly different between diabetic and non-diabetic patients. In contrast, some retrospective studies have found diabetes to be an independent predictor for early postoperative death.[5,6,10,11]

Beyond the initial 5 years of follow-up after CABG, cardiac mortality was evidently higher in diabetic patients than in non-diabetic patients, as demonstrated by the divergence in the survival curves (Fig. 2B). This may be explained by the ongoing deleterious effects of diabetes on the cardiovascular system which include endothelial dysfunction, pro-inflammatory and prothrombotic effects, which in turn perpetuate atherosclerosis and progression of coronary artery disease in native vessels, especially distal to the bypass grafts. These effects cannot be prevented by revascularisation of coronary arteries alone. Our overall survival rates at 20 years (35.4 ± 2.5% in diabetics and 48.9 ± 2.9% in non-diabetics) compare favourably to that described in another report (DM 23%, non-DM 42%, $P < 0.01$). From the same study, the median life expectancy following CABG was 13.7 years in diabetic patients and 17.9 years in non-diabetic patients.[12]

The overall 20-year survival rates in the propensity-matched group were 35.4 ± 2.5% in diabetics and 48.9 ± 2.9% in non-diabetics ($P < 0.001$). In the unmatched group, the overall 20-year survival rates were 30.9 ± 1.6% in diabetics and 49.2 ± 1.0% in non-diabetics ($P < 0.001$). In the propensity-matched group, freedom from cardiac mortality at 20 years was 57.8 ± 3.0% in diabetics and 70.2 ± 2.9% in non-diabetics ($P = 0.001$). In the unmatched cohort, freedom from cardiac mortality at 20 years was 56.0 ± 2.0% in diabetic patients and 68.4 ± 1.0% in non-diabetic patients ($P < 0.001$). Compared to the propensity-matched groups, analysis of the unmatched cohort appeared to underestimate the overall survival rate (30.9% vs 35.4%) and freedom from cardiac death (56.0% vs 57.8%) of diabetic patients. These differences in results were most probably due to the baseline differences between diabetic and non-diabetic patients. Patients with diabetes had a higher prevalence of comorbidities which were associated with a worse prognosis. As a result, the survival outcomes of diabetic patients based on unmatched data were confounded and erroneously worse than what they should be. The use of propensity score matching in this study allowed for correction of these biases arising from the use of non-randomised data.

Diabetic patients face an increased risk of postoperative wound infections following CABG and it has been demonstrated that strict perioperative glucose control lowers the risk of postoperative wound infection in these patients.[5,13-15] Apart from DM, other predictors of late cardiac-related mortality identified in our study (age, smoking and history of MI) have been reported previously.[16] Diabetic patients have a higher incidence of perioperative and late postoperative stroke. In our study, the incidence of fatal stroke during follow-up was 2.5 times higher ($P = 0.039$) in diabetic patients compared to non-diabetics. In an analysis of data from the FREEDOM trial, Domanski et al[17] reported that renal insufficiency (hazard ratio (HR): 3.57), baseline low-density lipoprotein ≥105 mg/dl (HR: 3.28) and baseline diastolic blood pressure (each 1 mm Hg increase reduces stroke hazard by 5%; HR: 0.95), were independent late stroke predictors in diabetic patients undergoing CABG for multivessel coronary artery disease.

Our study shows that diabetic patients have worse long-term survival and lower freedom from cardiac death after CABG than non-diabetic patients. The poorer survival of diabetics than non-diabetics is due to both non-cardiac deaths and excessive cardiovascular mortality. This finding concurs with most published studies.[4,9,10,18] In a large study of 39,235 patients with a mean follow-up of 5.9 ± 3.2 years, patients with insulin-dependent DM had more than double (HR: 2.04; 95% CI, 1.72 to 2.42) the long-term risk of all-cause death after CABG compared with patients without diabetes. The long-term risk of death in patients with non-insulin-dependent DM was only slightly increased (HR: 1.11; 95% CI, 1.05 to 1.18).[19] In another study following 856 diabetic patients who had undergone CABG up to 10 years, the relative risk of death or having an acute myocardial infarction (AMI) was 1.8 (95% CI, 1.5 to 2.2) in insulin-treated patients and 1.4 (95% CI, 1.2 to 1.7) in patients on oral medication. No increased risk of late death or AMI was observed in diet-treated patients with diabetes compared with patients without diabetes.[20] However, in 1 retrospective report of 767 diabetic patients with multivessel disease undergoing isolated first CABG, there was no significant difference in long-term survival in diabetic and non-diabetic patients who survived beyond the first 30 postoperative days.[6] In a study from China

examining the economic impact of diabetic patients who underwent CABG, costs for diabetic patients at 2 years follow-up were approximately S$2142 higher than for non-diabetic patients (P <0.001).[9]

Data from large registries has shown that arterial grafts significantly improve survival in CABG patients, especially if a LIMA-LAD graft was constructed.[21,22] Other authors have shown a better long-term outcome in diabetic patients if one or two internal thoracic artery grafts were used.[23,24] Compared with single internal mammary artery (IMA) grafting, bilateral IMA grafting in a propensity score-matched cohort of 828 patients with diabetes showed improved long-term survival without any increase in perioperative morbidity or mortality, in particular, sternal wound infections.[25] Although LIMA-LAD grafts could potentially improve outcomes for patients with diabetes, and 85% of our matched sample received them, the associated survival advantage conferred upon diabetic patients was not large enough to render the survival rates of diabetic and non-diabetic patients similar.

During the study period, the proportion of patients receiving LIMA-LAD grafting (73.1%) was much lower than our current institutional practice. With increasing evidence in the last decade demonstrating the long-term graft patency and survival benefit associated with LIMA-LAD grafting, this technique is now performed as frequently as possible in our patients undergoing isolated CABG, with current utilisation rates approaching 100%. In a study of long-term graft patency in diabetic patients, late angiographic evaluation of 269 patients (83/269, (30.9%) diabetic) at a mean of 7.7 ± 1.5 years after CABG showed that the proportion of complete graft occlusion was significantly lower in radial artery grafts (4.8%) than in saphenous vein grafts (25.3%) (P = 0.0004). The authors concluded that the use of the radial artery should be strongly considered in diabetic patients undergoing coronary bypass surgery, especially with high-grade target vessel stenosis.[26] One-year rates of vein graft failure were similar in patients with and without diabetes but among diabetics, it tended to be higher in those who received insulin compared with those who did not.[7]

Strengths and Limitations

The strengths of this study include its large sample size, extensive period of clinical follow-up and completeness of long-term survival data. As this is a retrospective observational study, inherent biases in data collection were inevitable. We did not investigate the difference in outcomes between patients with insulin dependent and non-insulin dependent DM. This study was also not designed to investigate the incidence of coronary re-interventions (PCI, redo-CABG), hospital readmissions or bypass graft patency. During the follow-up period of this study, treatment for coronary artery disease has changed and so has the risk profile of the patient population. Patients undergoing CABG today tend to be older and sicker with a wider range of medical comorbidities. The results of this study form an important baseline for future comparison, although they may no longer be generalisable to our patient population today.

Conclusion

This study reports the long-term survival and freedom from cardiac death of 5720 patients (1977 diabetics), who underwent isolated first CABG for multivessel coronary artery disease. Propensity score matching of 1122 patients (561 pairs) was performed to yield comparable groups. In conclusion, in-hospital mortality after CABG was low at 2% and did not differ significantly between diabetics and non-diabetics. In contrast, long-term survival was significantly impaired in diabetic patients, due to an excess of both cardiac and non-cardiac mortality. Aggressive treatment of DM, coexisting cardiovascular risk factors and cessation of smoking are essential measures to improve long-term survival in diabetic patients.

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Original Article

Long-Term Oncological Safety of Minimally Invasive Hepatectomy in Patients with Hepatocellular Carcinoma: A Case-Control Study

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Abstract

Introduction: Minimally invasive hepatectomy (MIH) for patients with hepatocellular carcinoma (HCC) is technically challenging, especially with large posteriorly located tumours or background of liver cirrhosis. This is a case-control study comparing the long-term oncological safety of HCC patients who underwent MIH and open hepatectomy (OH). Most of these patients have liver cirrhosis compared to other studies. Materials and Methods: Sixty patients were divided into 2 groups, 30 underwent MIH and 30 underwent OH for HCC resection. The patients in both groups were matched for extent of tumour resection, age and cirrhosis status. Patient characteristics, risk factors of HCC and all oncological data were studied. Results: Negative resection margins were achieved in 97% of patients in both groups. The mean blood loss during surgery was significantly lower in the MIH group compared to the OH group (361 mL vs 740 mL; 95% CI, 222.2, 734.9; *P* = 0.04). Hospitalisation is significantly shorter in MIH group (7 days vs 11 days; 95% CI, 6.9, 12.2,; *P* = 0.04). Eight patients (27%) in the MIH group and 13 patients (43%) in the OH group developed HCC recurrence (*P* = 0.17). One, 3 and 5 years disease-free survival between MIH and OH groups are 76% vs 55%, 58% vs 47%, and 58% vs 39% respectively (*P* = 0.18). One, 3 and 5 years overall survival between MIH and OH groups are 93% vs 78%, 89% vs 70%, and 59% vs 65% respectively (*P* = 0.41). Conclusion: MIH is a safe and feasible curative treatment option for HCC with similar oncological outcomes compared to OH. MIH can be safely performed to remove tumours larger than 5 cm, in cirrhotic liver, as well as centrally and posterior located tumours. In addition, MIH patients have significant shorter hospitalisation and intraoperative blood loss.

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Key words: Laparoscopy, Liver cirrhosis, Primary liver cancer

Introduction

Minimally invasive hepatectomy (MIH) is well established and routinely done for benign and malignant hepatic lesions in suitable cases.[1] The advancements in video systems, energy devices and stapling equipment[2] in recent years have also made it feasible and safe for malignant hepatic lesions.[3,4]

However, the development and adoption of MIH compared to other forms of minimally invasive surgery has been slow due to the concerns regarding the adequacy of oncologic clearance, achievement of haemostasis, length of operating time, risk of gas embolism[5] and the lack of randomised controlled trials.

In addition, the management of hepatocellular carcinoma (HCC) remains a major challenge to all hepatobiliary surgeons, especially in patients with a background of liver cirrhosis.[6,7] These patients have poorer preoperative status, lower hepatic reserves and higher rates of HCC recurrence, and curative resection is not always possible.

Therefore, few centres worldwide currently offer MIH for HCC, and the majority of hepatectomy studied in published papers are wedge resections and left lateral sectionectomies.[1] The role of MIH in more challenging hepatectomies such as hemihepatectomy and posterior sectionectomy, even in patients with a background of liver cirrhosis, has not been very well documented.

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This paper aims to study the oncological outcomes of MIH performed for HCC compared to open hepatectomy (OH) in a tertiary centre with a full spectrum of capabilities for MIH in Singapore. Most of the patients studied have cirrhosis, and some underwent minimally invasive surgery for challenging hepatectomy.

Materials and Methods

Patient Selection

More than 100 cases of MIH for benign and malignant liver diseases at a university hospital with advanced laparoscopic facilities and liver transplant services were retrospectively studied. Thirty consecutive patients who underwent MIH for HCC over a period of 54 months (August 2006 to February 2011) were included in this study. They were matched for extent of tumour resection, age and cirrhosis status with 30 patients who underwent OH for HCC mostly during a similar period. Presence of liver cirrhosis and portal hypertension was determined by preoperative imaging (mainly computed tomography [CT] or magnetic resonance imaging [MRI]), and all cases were discussed in our multidisciplinary tumour board meeting.

The extent of resection was classified as minor resection (wedge resection and single segment resection), partial resection (2 to 3 liver segments resection) and major resection (4 or more liver segments resection) for matching purposes. This classification is chosen for matching because it is widely recognised that morbidity and mortality rate is inversely proportionate to remnant liver volume.[8]

Data Collection

Patient data recorded include age and gender, risk factors for HCC, presence of comorbidities, presence of liver cirrhosis and portal hypertension changes on preop imaging, cirrhosis status, Ishak's fibrosis score on histology of the resected specimen and the Child-Pugh classification.

Operative data recorded include surgical approach (fully laparoscopic or hand-assisted), extent of resection, operative time, blood loss, blood transfusion required, need for conversion, presence of complications, days to ambulation, length of hospitalisation and treatment for recurrence.

Oncologic data recorded includes tumour size and location, resection margins, histological features (tumour differentiation, and capsular, perineural/lymphatic/vascular involvement), multifocality and time to HCC recurrence, follow-up period and survival status.

The oncological and surgical outcomes were compared between the patients who underwent MIH and OH. The patients who developed HCC recurrence in both groups were also studied to look for differences in risk factors for recurrence, such as tumour size, resection margins, histological features, age and gender and cirrhosis status.

Data Analysis

All data was analysed with SPSS software, through which continuous variables were compared using the Mann-Whitney U test and categorical variables using the Chi-square test. Disease-free and overall survival periods were analysed with the Kaplan-Meier test; 95% confidence interval (CI) was calculated for continuous variables. Statistical significance was defined as $P < 0.05$.

Results

Patient Data

There was a majority of male patients, patients with a background of liver cirrhosis, patients with Child's A status and Hepatitis B carriers in both groups. There is no statistically significant difference in cirrhosis and portal hypertension changes on preop imaging, Ishak's fibrosis score on the resected specimens and preop Child's score. Table 1 shows the patients' characteristics.

Operative Data

Within the group of patients who underwent MIH, 10 patients (33%) had a minor resection, 14 patients (47%) had a partial resection and 6 patients (20%) had a major resection. Thirteen patients (43%) had fully laparoscopic hepatectomy and 17 patients (57%) had hand-assisted laparoscopic hepatectomy.

The extent of resection and cirrhosis status are identical and the age distribution is similar in the group of patients who underwent OH compared to the group who underwent MIH, as a result of patient matching.

The mean intraoperative blood loss was significantly lower in the MIH group compared to the OH group (361.5 ± 376.9 mL vs 740.0 ± 1106.6 mL; 95% CI, 222.2, 734.9; $P = 0.04$). The patients in the MIH group also had a shorter length of hospitalisation compared to those in the OH group (7.0 ± 3.0 days vs 11.0 ± 9.3 days; 95% CI, 6.9, 12.2; $P = 0.01$). There was no statistically significant difference in the mean operative time between the patients in the MIH and OH groups (288 vs 301 minutes; 95% CI, 244.7, 299.5; $P = 0.15$). Table 2 shows operative variables in both groups.

Oncological Data

All resected specimens in both MIH and OH groups were proven to be HCC after histological examination. The median tumour size was also similar between both groups, 33 mm (14-120) vs 43 mm (11-140); 95% CI, 34.8, 50.7; $P = 0.18$.

Table 1. Patient Characteristics

	MIH, n = 30	OH, n = 30	*P* Value	95% CI
Mean age, years (SD)	60 (± 9.7)	58 (± 11.6)	0.28	57.5 – 63.1
Male, n (%)	22 (73%)	25 (83%)	0.35	NA
Features of cirrhosis on preop imaging, n (%)	20 (67%)	20 (67%)	1.00	NA
Features of portal hypertension on preop imaging, n (%)	15 (50%)	8 (27%)	0.15	NA
Ishak's fibrosis score			0.22	NA
F0 – F3, n (%)	12 (40%)	17 (57%)		
F4, n (%)	7 (23%)	6 (20%)		
F5, n (%)	5 (17%)	3 (10%)		
F6, n (%)	6 (20%)	4 (13%)		
Child's status			0.45	NA
A, n (%)	27 (90%)	26 (87%)		
B, n (%)	2 (7%)	4 (13%)		
C, n (%)	1 (3%)	0 (0%)		
Risk factors			0.68	NA
Hepatitis B, n (%)	20 (67%)	25 (83%)		
Hepatitis C, n (%)	3 (10%)	1 (3.5%)		
Others, n (%)	4 (13%)	3 (10%)		
None, n (%)	3 (10%)	1 (3.5%)		

MIH: Minimally invasive hepatectomy; NA: Not applicable; OH: Open hepatectomy

Table 2. Operative Variables

	MIH	OH	*P* Value	95% CI
Surgical technique			NA	NA
Fully laparoscopic, n (%)	13 (43%)	NA		
Hand-assisted laparoscopic, n (%)	17 (57%)	NA		
Type of resection			NA	NA
Minor, n (%)	10 (33%)	10 (33%)		
Partial, n (%)	14 (47%)	14 (47%)		
Major, n (%)	6 (20%)	6 (20%)		
Extent of resection			NA	NA
Central hepatectomy	0 (0%)	1 (3.3%)		
Right hepatectomy	2 (6.7%)	3 (10%)		
Left hepatectomy	2 (6.7%)	2 (6.7%)		
Left lateral sectionectomy	6 (20%)	5 (16.7%)		
Right anterior sectionectomy	0 (0%)	1 (3.3%)		
Right posterior sectionectomy	6 (20%)	5 (16.7%)		
Posterior-superior segmentectomy/wedge resection (seg. 7-8)	3 (10%)	4 (13.3%)		
Anterior-lateral segmentectomy/wedge resection (seg. 2-6)	11 (36.7%)	9 (30%)		
Anatomical resection, n (%)	27 (90%)	26 (87%)	0.86	NA
Mean operative time, minutes (SD)	288 (± 178)	301 (± 108)	0.15	244.7 – 299.5
Mean blood loss, mL (SD)	361.5 (± 376.9)	740 (±1106.8)	0.04	222.2 – 734.9
Mean length of hospitalisation, days (SD)	7 (± 3)	11 (± 9.3)	0.01	6.9 – 12.2

MIH: Minimally invasive hepatectomy; NA: Not applicable; OH: Open hepatectomy

Table 3. Specimen Characteristics, Recurrence during Follow-up

	MIH	OH	*P* Value	95% CI
Median tumour size, mm (range)	33 (14 - 120)	43 (11 - 140)	0.18	34.8 – 50.7
Resection margin			0.24	
Median, mm (range)	8.9 (0-30)	4.2 (0 - 52)		6.5 – 11.6
>10 mm, n (%)	11 (37%)	10 (33%)		
1 mm – 10 mm, n (%)	18 (60%)	19 (64%)		
Positive, n (%)	1 (3%)	1 (3%)		
Differentiation			0.52	NA
Well, n (%)	11 (37%)	8 (27%)		
Moderate, n (%)	18 (60%)	21 (70%)		
Poor, n (%)	1 (3%)	1 (3%)		
Vascular invasion, n (%)	3 (10%)	4 (13.3%)	0.58	NA
Perineural/lymphatic involvement, n (%)	5 (17%)	6 (20%)	0.67	NA
Capsular involvement, n (%)	4 (13%)	6 (20%)	0.49	NA
Multifocality, n (%)	1 (3.3%)	2 (6.7%)	0.78	NA
Overall recurrence, n (%)	8 (27%)	13 (43%)	0.17	NA
Recurrence in non-anatomical resection	0 (0%)	1 (7.7%)	0.33	NA
Median time to recurrence, months (range)	9.1 (6.2 - 33.4)	8.5 (1.2 - 47.8)	0.29	2.3 – 17.2
Median follow-up period, months (range)	42.5 (3 - 71)	36.5 (0 - 113)	0.73	21.1 – 43.4

MIH: Minimally invasive hepatectomy; NA: Not applicable; OH: Open hepatectomy

Negative resection margins were achieved in 97% of patients in both groups, with median resection margins of 8.9 mm (0-30) and 4.2 mm (0-52) for the MIH and OH groups respectively (95% CI, 6.5, 11.6; $P = 0.24$).

There were no statistically significant differences in histological features (tumour differentiation, multifocality and capsular, perineural/lymphatic/vascular involvement) between the MIH and OH groups.

The median follow-up period of the MIH and OH groups were 42.5 and 36.5 months respectively (95% CI , 21.1, 43.4; $P = 0.73$). Table 3 shows the specimen characteristics and recurrence during follow-up in both groups. Figures 1 and 2 illustrate the tumour location in both groups.

During the follow-up, 8 patients (27%) in the MIH group and 13 patients (43%) in the OH group developed HCC recurrence ($P = 0.17$). The mean time to recurrence was 15.5 ± 9.2 and 13 ± 13.5 months for those in the MIH and OH groups respectively (95% CI, 2.3, 17.2; $P = 0.29$). There were no statistically significant differences between these MIH and OH groups in mean tumour size (43.2 ± 24.0 vs 64.4 ± 37.6 mm; 95% CI, 42.7, 87.1; $P = 0.06$) and median resection margins (4.5 mm (0-18) vs

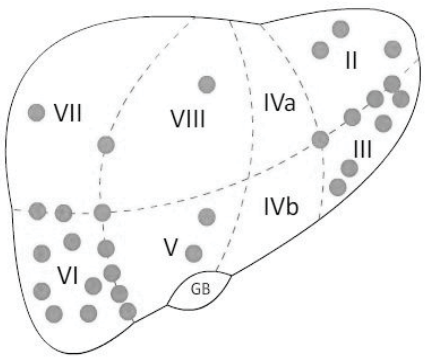


Fig. 1. Tumour locations in patients from the MIH group.

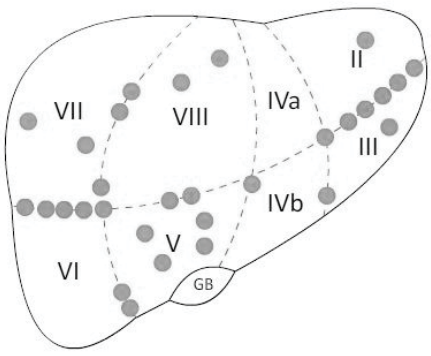


Fig. 2. Tumour locations in patients from the OH group.

Table 4. Comparison of Risk Factors for Recurrence

	MIH	OH	*P* Value	95% CI
n (%)	8 (27%)	13 (43%)	0.17	NA
Mean tumour size, mm (SD)	43.2 (± 24)	64.4 (± 37.6)	0.06	42.7 – 87.1
Resection margin				
Median, mm (range)	4.5 (0 - 18)	3.4 (0 - 35)	0.29	0.1 – 6.7
>10 mm, n (%)	1 (11%)	2 (14%)		
1 mm – 10 mm, n (%)	7 (78%)	11 (79%)		
Positive, n (%)	1 (11%)	1 (7%)		
Perineural/vascular/lymphatic involvement, n (%)	3 (38%)	4 (31%)	0.67	NA
Capsular involvement, n (%)	1 (13%)	2 (15%)	0.58	NA
Cirrhosis, n (%)	5 (63%)	8 (62%)	0.33	NA
Mean age, years (SD)	62 (± 10.7)	54 (± 12.8)	0.07	46.3 – 61.8
Male, n (%)	7 (88%)	13 (100%)	0.36	NA

MIH: Minimally invasive hepatectomy; NA: Not applicable; OH: Open hepatectomy

3.4 mm (0-35); 95% CI, 0.1, 6.7; $P = 0.29$). There was 1 patient with a positive resection margin in each group. There were also no statistically significant differences in the histological features, age, gender and cirrhosis status. One non-anatomical resection in OH group developed recurrence, but it did not reach statistical significance when compared to MIH group. Table 4 shows the comparison of risk factors for recurrence in patients in both groups who developed recurrence.

One, 3 and 5 years disease-free survival between MIH and OH groups are 76% vs 55%, 58% vs 47%, and 58% vs 39% respectively ($P = 0.18$). One, 3 and 5 years overall survival between MIH and OH groups are 93% vs 78%, 89% vs 70%, and 59% vs 65% respectively ($P = 0.41$). Figures 3 and 4 illustrate the Kaplan-Meier curves for disease-free survival and overall survival of both groups.

Discussion

Current Literature on Minimally Invasive Hepatectomy

Minimally invasive surgery has been gradually replacing open surgery in many cases, as it offers better surgical outcomes like reduced intraoperative bleeding,[9,10] shorter hospital stays,[4,10] reduced postoperative pain and faster recovery of surgical wounds and normal physical function.[11,12] With increasing experience, surgeons are also able to achieve comparable operative times[8,12] and complication rates.[13]

MIH has become a more established curative treatment option for HCC over the last decade.[1,4,14] However, it is performed in few centres worldwide as it is technically challenging compared to other forms of minimally invasive surgery. A good amount of surgical experience and advanced laparoscopic equipment are required.

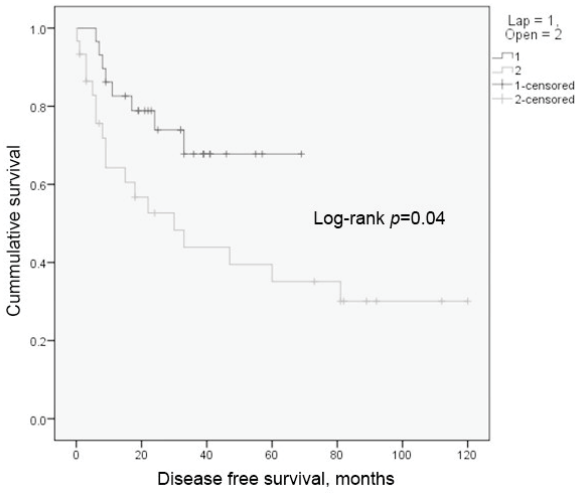
Most of the published literature[15-19] are generic studies on the feasibility of MIH in patient populations with variable demographics and disease characteristics. Our study, done in a tertiary hospital in Singapore, focuses on the oncological outcomes of MIH in patients with HCC and liver cirrhosis.

Experience with Minimally Invasive Hepatectomy

Our centre is a regional referral centre for liver transplantation and a variety of liver diseases, and possesses a full spectrum of capabilities for MIH; 67% of the patients in our study have HCC on a background of liver cirrhosis, which is representative of the patient profile locally.

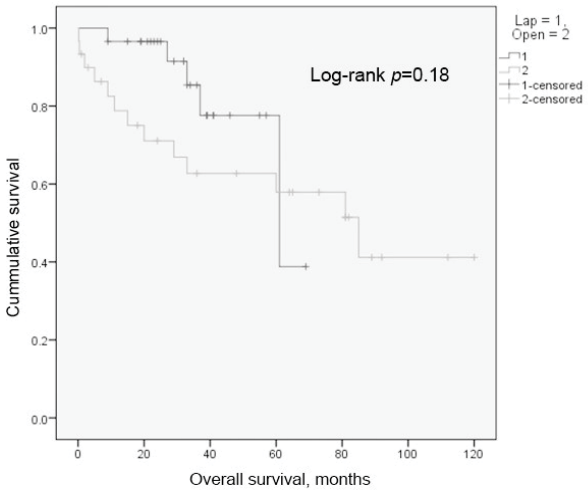
Haemostasis in MIH has always been a concern, especially in patients with liver cirrhosis and poor liver function.[7, 20] However, a series of reports have shown that surgical and oncological outcomes are comparable with that of OH in the hands of experienced surgeons.[3,6,11,21] Furthermore, the use of laparoscopic energy devices and stapling devices help in the dissection of liver parenchyma and ligation of big vascular pedicles respectively.[2]

The liver is routinely assessed in our centre with laparoscopic ultrasound devices during the operation before hepatectomy is performed. This is the gold standard in both MIH and OH in most centres as intraoperative ultrasound (IOUS) has been shown to be more sensitive than MRI and CT scans for detecting lesions smaller than 5 mm in size.[22] In this study, we did not detect any extra lesions in both MIH and OH groups with IOUS, hence no change in surgical strategy intraoperatively.



Disease-free Survival	1 Year	3 Year	5 Year	Log-rank *P* Value
MIH	76%	58%	58%	0.18
OH	55%	47%	39%	

Fig. 3. Graph and table showing the disease-free survival (MIH: "Lap", OH: "Open").



Overall Survival	1 Year	3 Year	5 Year	Log-rank *P* Value
MIH	93%	89%	59%	0.41
OH	78%	70%	65%	

Fig. 4. Graph and table showing the overall survival (MIH: "Lap", OH: "Open").

Superior Surgical Outcomes

In our series of patients, some of whom underwent resection of large and posteriorly located tumours via MIH, no conversion to laparotomy was required. In addition, the patients who underwent MIH had a significantly reduced intraoperative blood loss and shorter length of hospitalisation. The mean operative time was also not significantly different.

Some studies do not recommend MIH for tumours exceeding 50 mm,[3,6,8,23] as ideal candidates for MIH are conventionally thought to be patients with small and peripherally located tumours. In our study, 30% of the MIH cases involved posterior part of the liver and 13.4% were major liver resection. In addition to that, we had 6 patients with tumours larger than 50 mm and up to 120 mm who underwent MIH. There is no significant difference in tumour size and location in MIH and OH groups. This initial results show that with proper preoperative planning and use of appropriate surgical devices and technique, MIH can be safely performed in most types of liver resection by experienced hepatobiliary surgeons in patients with HCC and liver cirrhosis.

Comparable Oncological Outcomes

In our series of patients, MIH was shown to be comparable to OH in terms of oncological outcomes. Both groups of patients who underwent either MIH or OH for resection of HCC had similar patient profiles, tumour size, location and histological features. There were no significant differences in the 3-year and 5-year overall survival rates between the 2 groups.

In addition, our centre achieved negative resection margins in 97% of patients in both groups with a mean margin of 9 mm. This result is highly encouraging given that adequate resection margins is a major concern among hepatobiliary surgeons for HCC resection. The proportion of our patients who developed HCC recurrence in both groups was also similar, and there were no cases of port-side recurrence in those who underwent MIH. There was 1 patient in each group who had positive resection margins, and both patients subsequently developed HCC recurrence.

The standard surgical resection margins for HCC remains widely debatable across the world. There are suggestions that bigger margins do not contribute to longer survival and lower HCC recurrence rates in cases that achieved microscopic negative margins.[6,7] Furthermore, there are concerns that unnecessary extension of margins may compromise liver function in patients who have poor liver reserves preoperatively.[20]

The comparable oncological outcomes in our study clearly show that in a highly specialised centre, MIH is not an inferior curative treatment option for HCC and does not compromise oncological resection in all kinds of

hepatectomy compared to OH, even in patients with liver cirrhosis. However, we believe that performing MIH for HCC resection is technically demanding and should be done only by experienced surgeons.

This study is limited by its retrospective nature, small number of patient as well as unmatched tumour location. However, the results demonstrated that MIH can be performed in large tumour, posteriorly or superiorly located tumours and cirrhotic liver. We were able to perform anatomical resection laparoscopically in majority of the cases. We hope to see well designed randomised controlled trials comparing MIH and OH for cirrhotic patients with HCC in the near future to further conclude the oncologic safety of MIH.

Conclusion

MIH is a safe and feasible curative treatment option for HCC with similar oncological outcomes compared to OH. MIH can be safely performed to remove tumours larger than 5 cm, in cirrhotic liver, as well as centrally and posterior located tumours. In addition, MIH patients have significant shorter hospitalisation and intraoperative blood loss.

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Review Article

A Practical Guide to Ordering and Interpreting Coagulation Tests for Patients on Direct Oral Anticoagulants in Singapore*

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Abstract

Introduction: Direct oral anticoagulants (DOACs) are establishing themselves as principle choices for the treatment of a variety of thrombotic disorders. DOACs are also known to affect common coagulation tests which are routinely performed for patients in clinical practice. An understanding of their varied effects is crucial for the appropriate ordering of coagulation tests and their interpretation. Materials and Methods: Laboratories in public and private healthcare institutions and commercial sectors were surveyed on coagulation tests offered and their methods. A Medline and bibliography search, including a search on search engines, was performed for publications reporting the effects of dabigatran, apixaban and rivaroxaban on these coagulation tests. These papers were reviewed and summarised for consensus recommendations. Results: Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are variably affected by the DOACs and dependent of the coagulation assays used. Clinicians must know which laboratory has performed these tests to logically interpret test results. A normal PT or aPTT does not exclude the presence of residual DOACs effect. The thrombin time is sensitive to dabigatran but not apixaban or rivaroxaban. Specialised coagulation tests such as thrombophilia tests are also variably affected by the DOACs. All laboratories in Singapore however, employ similar test methods permitting a common set of recommendations for specialised coagulation testing. Conclusion: Knowledge of the effects of DOACs on coagulation testing is essential to determine the appropriateness of performing such tests and interpreting them coherently. Practical recommendations which are tests and location-specific are set out in this paper.

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Key words: Apixaban, Dabigatran, Laboratory testing, Rivaroxaban

Introduction

Direct oral anticoagulants (DOACs) describe 2 classes of oral anticoagulants that target thrombin (oral direct thrombin inhibitors) (DTI) and factor Xa (anti-FXa), both of which have been rapidly changing the anticoagulation landscape. Their adoption as viable alternatives to conventional vitamin K antagonist such as warfarin have been fomented by clinical trial data indicating at least equivalence in efficacy and safety when compared to standard anticoagulants for a variety of indications.[1-10] The added benefits of fixed dosing as well as the limited drug and food interactions without the need for routine monitoring has contributed to an increasing number of patients taking these anticoagulants.[11] There are currently 3 DOACs registered in Singapore for a variety of indications as listed in Table 1. Dabigatran, a DTI, binds competitively and reversibly to the active site on free- and clot-bound thrombin.[12] Rivaroxaban and apixaban are competitive anti-FXa that bind to both free- and clot-bound factor Xa.[12]

As DOACs primarily interrupt thrombus formation via the inhibition of downstream coagulation proteins, they can potentially interfere with many commonly available

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Table 1. DOACs Approved in Singapore and Their Indications

Drug	Class	Approved Indications
Dabigatran (Boehringer Ingelheim, Germany)	Direct thrombin inhibitor	1. VTE prophylaxis in major orthopaedic surgery. 2. Treatment of acute DVT and PE. 3. Prevention of recurrent DVT and PE 4. Stroke and systemic embolism prevention in non-valvular atrial fibrillation.
Apixaban (Pfizer/Bristol Myers Squibb, USA)	Factor Xa inhibitor	1. VTE prophylaxis in major orthopaedic surgery. 2. Treatment of acute DVT and PE. 3. Prevention of recurrent DVT and PE. 4. Stroke and systemic embolism prevention in non-valvular atrial fibrillation.
Rivaroxaban (Bayer Pharma AG, Germany)	Factor Xa inhibitor	1. VTE prophylaxis in major orthopaedic surgery. 2. Treatment of acute DVT and PE. 3. Prevention of recurrent DVT and PE. 4. Stroke and systemic embolism prevention in non-valvular atrial fibrillation. 5. Prevention of cardiovascular deaths after acute coronary syndrome.

DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism

routine and specialised coagulation assays and influence their interpretation.[13] The degree of interference is dependent on the DOACs used and their plasma levels at the time of sample collection. Interference is also governed by the test methods and sensitivity of the assays used in individual laboratories.[14] Since the information provided on the patient to clinical laboratories is generally scanty, laboratories cannot assist clinicians with interpretation of test results. Clinicians therefore need to be aware of the influences of DOACs on coagulation testing in order to make informed choices when considering the appropriateness of tests for their patients and permit accurate interpretation. More importantly, this knowledge needs to be up-to-date and specific to the institution or laboratories that perform these tests. Currently, most laboratories in Singapore do not publish their laboratory-specific guides on this matter nor have the effective means of communicating this with their doctor-clients. This paper aims to address this gap in information on coagulation testing for patients taking DOACs in Singapore and is intended to provide a clinician-centric and laboratory-specific guide for our clinicians.

Materials and Methods

The test methodology and reagents used for routine and specialised coagulation tests by the major haematology laboratories in Singapore in 2015 were surveyed by contacting each laboratory individually. Laboratories that participated in this survey were: Singapore General Hospital (SGH), Tan Tock Seng Hospital (TTSH), National University Hospital (NUH), Changi General Hospital (CGH), Khoo Teck Puat Hospital (KTPH), KK Women's and Children's Hospital (KKWCH), Ng Teng Fong Hospital (NTFH), Sengkang Hospital (SKH), Parkway Laboratory Services (PLS), Mount Alvernia Hospital (MAH), Quest Laboratory, Innovative Diagnostics and Raffles Diagnostics. Coagulation tests offered and methods used in laboratories at SingHealth and National Healthcare Group polyclinics were also determined.

The effects of dabigatran, rivaroxaban and apixaban on each laboratory's routine and specialised coagulation tests were obtained by reviewing product inserts and through a literature search performed on Medline and search engines including Google. The key words "dabigatran", "rivaroxaban", "apixaban", "coagulation", "laboratory", "test", "assay" as well as names of individual tests were used during the search. Relevant papers which reported the effects of the DOACs on tests and assays used in our hospitals were subjected to further review and summarised. The bibliographies of selected papers were also searched for papers that may have eluded the Medline search. Information gathered was reviewed by all authors for their concordance of DOACs' effects on the tests in question. Unpublished validation studies of local laboratories were used to supplement published findings if available.

The tests categorised as routine were the prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin clotting time (TCT), fibrinogen and D-dimers. These tests are performed by general haematology or core laboratories with high through-puts and mostly available around the clock in the major hospitals. The listed tests are offered by all the surveyed laboratories. Specialised coagulation tests, on the other hand, are performed in a limited number of institutions and mostly available during office hours with batched testing. These included testing for lupus anticoagulants, clotting factors and von Willebrand factor assays, normal plasma mixing studies, and thrombophilia markers (protein C, protein S, antithrombin, activated protein C resistance). Currently, only the laboratories in SGH, TTSH and NUH perform these specialised coagulation tests. Requests for these tests made through other laboratories are usually outsourced to these 3 laboratories.

Table 2. Routine Coagulation Tests and Reagents Used in Hospitals and Laboratories in Singapore

Test	Activator	Hospital/Laboratory
Prothrombin time (PT)	Dade Innovin	SGH,CGH, KTPH, PLS, QL, ID, RD, SKH
	Neoplastin C1 Plus	NUH, TTSH, NTFH, KKH, SHP, NHGP
	Thromborel S	MAH
Activated partial thromboplastin time (aPTT)	Actin FSL	SGH,CGH, KTPH, PLS, QL, ID, RD, MAH, SKH
	STA Cephascreen	NUH, TTSH, NTFH, KKH
Thrombin clotting time	Thromboclotin	SGH,CGH, KTPH, PLS, QL, ID, MAH, SKH
	STA Thrombin	NUH, TTSH, NTFH, KKH

CGH: Changi General Hospital; ID: Innovative Diagnostics; KKWCH: KK Women's and Children's Hospital; KTPH: Khoo Teck Puat Hospital; MAH: Mount Alvernia Hospital; NHGP: National Healthcare Group Polyclinics; NTFH: Ng Teng Fong Hospital; NUH: National University Hospital; PLS: Parkway Laboratory Services; QL: Quest Laboratory; RD: Raffles Diagnostics; SGH: Singapore General Hospital; SHP: Singhealth Polyclinics; SKH: Sengkang Hospital; TTSH: Tan Tock Seng Hospital

The summary recommendations in this paper were reviewed and affirmed by all authors with confirmation by individual laboratories for accuracy.

Results

Routine Coagulation Tests

The assays used by the various laboratories in Singapore for routine coagulation tests are shown in Table 2. For PT testing, the 3 reagents used are Innovin (Siemens Healthcare Diagnostics, Marburg, Germany), Thromborel S (Siemens Healthcare Diagnostics, Marburg, Germany) and Neoplastin C1 Plus (Diagnostica Stago S.A.S, Paris, France). These reagents were used on corresponding instruments from the same manufacturers. The number of papers that reported the effects of DOACs using at least 1 of these reagents were: dabigatran – 10,[15-24] rivaroxaban – 8,[17,19,21,25-29] apixaban – 3.[27,30,31] Dabigatran has minimal effect on PT irrespective of the reagents used. In contrast, rivaroxaban and apixaban prolong the PT test, but this effect is, however, dependent on the reagents employed. In fact, the test is more sensitive with the thromboplastin reagent Neoplastin C1 Plus, while with Thromborel S, it is least sensitive. For practical purposes, the interpretation of PT in the presence of DOACs based on the published literature and our clinical experiences are summarised as a decision tree (Fig. 1). Current PT reagents are less sensitive to apixaban as compared to rivaroxaban. In general, a normal PT result does not exclude the presence of residual anticoagulant effect for any of the DOACs.

Point-of-care (POC) PT monitoring devices such as the Coaguchek XS are affected by increasing doses of rivaroxaban and apixaban since its prothrombin time detection is also dependent on the human recombinant thromboplastin. This effect is more pronounced and linear with rivaroxaban than apixaban. Dabigatran, on the other hand, has limited effect on POC PT test results.[32] Currently, POC PT testing using the Coaguchek XS is offered by the major hospitals and all polyclinics in Singapore for the monitoring of patients on warfarin.

For aPTT testing, Actin FSL (Siemens Healthcare Diagnostics, Marburg, Germany) and STA Cephascreen (Diagnostica Stago S.A.S, Paris, France) are the 2 test reagents used in Singapore on corresponding instruments from the same manufacturers. The number of published papers that reported the effects of the DOACs by using at least 1 of these reagents were: dabigatran – 7,[15,17-20,23,33] rivaroxaban – 4,[17,19,21,25] apixaban – 3,[25,30,31]. In contrast to the PT assay, dabigatran prolonged aPTT in a more pronounced manner than the anti-Xa inhibitors. aPTT tests are generally insensitive to apixaban. The interpretation of aPTT for patients taking DOACs is summarised as a decision tree in Figure 2. As in the case of PT testing, a normal aPTT result does not exclude the presence of residual anticoagulant effect for any of the DOACs.

The thrombin clotting time (TCT) assay which is also commonly known as the thrombin time, directly measures the activity of thrombin in the plasma. It is therefore prolonged by the DTI, dabigatran.[20,23,34] A sharp linear dose-response curve is observed with increasing concentrations.[35] However, the maximal clotting limits is reached with relatively low dabigatran concentration making the TCT unsuitable for quantifying dabigatran concentration.[23,36] Slight differences in sensitivities between different instrument/reagent combinations among the labs in Singapore do not affect the generalisability of TCT results obtained. The TCT is best used to exclude the presence of dabigatran and a normal TCT in any of our institutions will indicate the absence of dabigatran in the test sample. Rivaroxaban and apixaban, which are anti-FXa, do not affect the TCT.

Assays used for fibrinogen testing in Singapore are not affected by any of the DOACs.[21] Their results may be

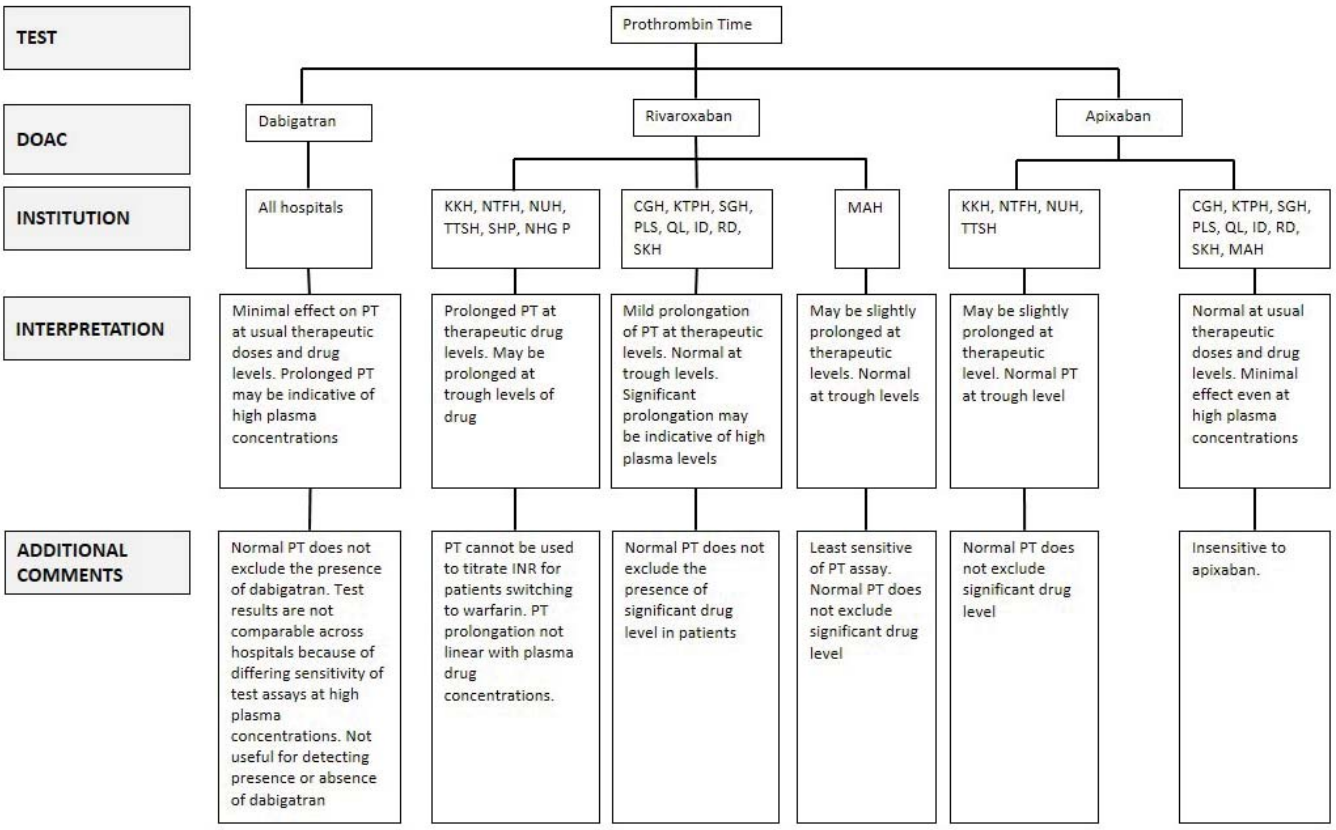

Fig. 1. Decision tree for interpreting prothrombin time in Singapore hospitals.
CGH: Changi General Hospital; DOAC: Direct oral anticoagulant; ID: Innovative Diagnostics; KKWCH: KK Women's and Children's Hospital; KTPH: Khoo Teck Puat Hospital; MAH: Mount Alvernia Hospital; NHGP: National Healthcare Group Polyclinics; NTFH: Ng Teng Fong Hospital; NUH: National University Hospital; PLS: Parkway Laboratory Services; PT: Prothrombin time; QL: Quest Laboratory; RD: Raffles Diagnostics; SGH: Singapore General Hospital; SHP: Singhealth Polyclinics; SKH: Sengkang Hospital; TTSH: Tan Tock Seng Hospital

interpreted independent of the use of DOACs. DOACs will also not interfere with D-dimer testing which is measured by immunoturbidity methods.

Specialised Coagulation Tests

The effect of DOACs on these specialised tests is generally determined by whether the assays are clot-based or chromogenic and whether thrombin or factor Xa is a substrate in the assays.[33,37-40] Specialised laboratories performing these tests in Singapore currently use a common platform with similar methods. The impact of DOACs on these tests are therefore generalisable to all institutions with no requirement for distinction between laboratories or instruments, unlike in the case of some routine tests as discussed earlier. Table 3 summarises the influence of DOACs on specialised testing, the types of common assays used in our laboratories in Singapore, and our recommendations in respect to the appropriateness of ordering these tests when a patient is taking a DOAC.

Discussion

This paper represents the collaborative effort of our Thrombosis Haemostasis Workgroup to address the current issues related to the interpretation of coagulation tests for the increasing number of patients taking DOACs in Singapore. By consolidating our current understanding of the effects of DOACs on coagulation tests into a practical reference document that is geared for both private and public institutions as well as community practice in Singapore, we hope to achieve a number of objectives. Firstly, the potential influence of DOACs on coagulation testing is currently not common knowledge to many generalist clinicians. This paper therefore serves to highlight this aspect of management and raise awareness among clinicians who should be mindful of such potential pitfalls. Awareness must however be accompanied by the availability of a handy resource for clinicians to check and interpret coagulation tests that are ordered for their patients. It is our intention for this paper to serve as this resource. Accurate interpretation

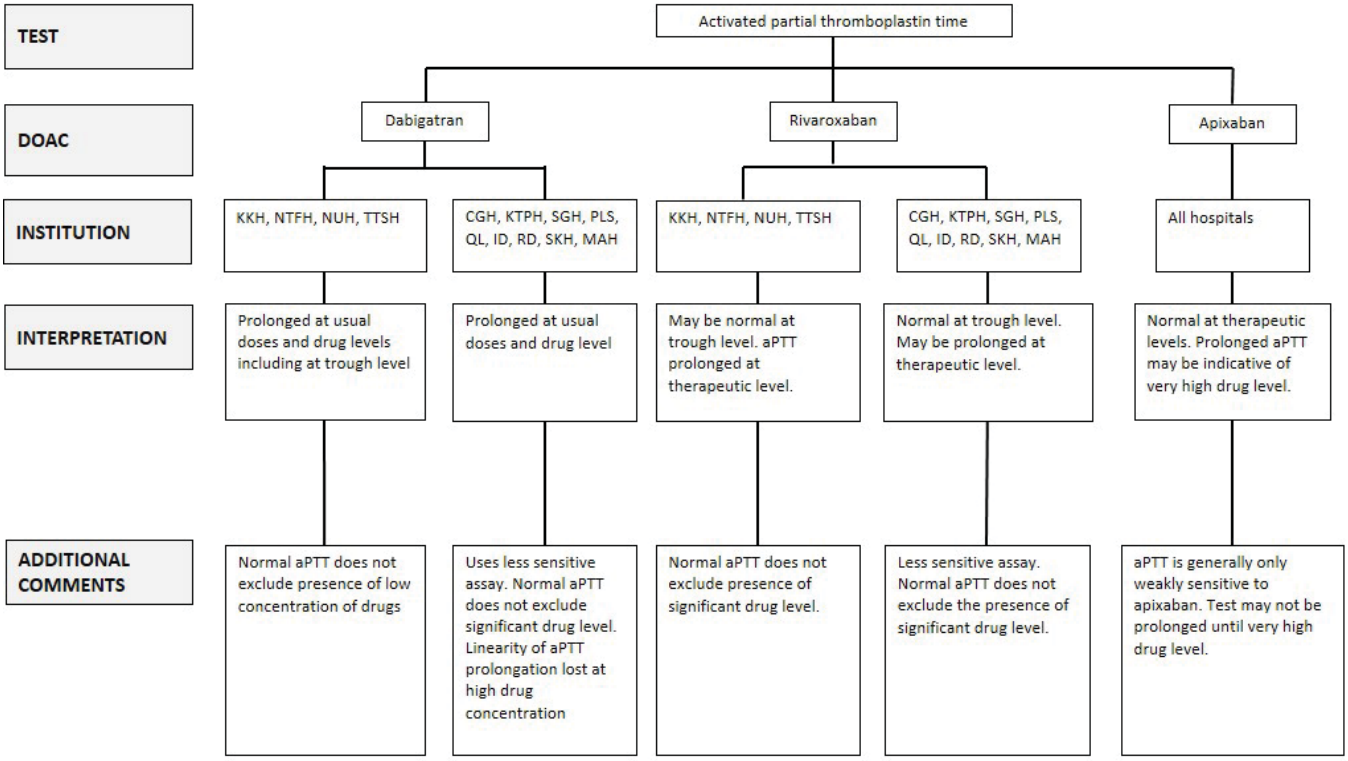

Fig. 2. Decision tree for interpreting activated partial thromboplastin time in Singapore hospitals.
aPTT: Activated partial thromboplastin time; CGH: Changi General Hospital; DOAC: Direct oral anticoagulant; ID: Innovative Diagnostics; KKWCH: KK Women's and Children's Hospital; KTPH: Khoo Teck Puat Hospital; MAH: Mount Alvernia Hospital; NHGP: National Healthcare Group Polyclinics; NTFH: Ng Teng Fong Hospital; NUH: National University Hospital; PLS: Parkway Laboratory Services; QL: Quest Laboratory; RD: Raffles Diagnostics; SGH: Singapore General Hospital; SHP: Singhealth Polyclinics; SKH: Sengkang Hospital; TTSH: Tan Tock Seng Hospital

of coagulation test results in patients on DOACs can have important implications in the management of patients especially those who are acutely ill. Key information must be available for accurate interpretation, such as the DOAC used, time of last dose, concomitant use of other drugs that might interfere with the DOAC pharmacokinetics and/or pharmacodynamics, and any comorbidities that could interfere with baseline routine coagulation tests such as the PT and APTT.

Another objective of this paper is to provide counsel on the appropriateness of performing specialised coagulation tests when a patient is taking DOACs. Our recommendation on the validity of these tests is intended to reduce false negative or false positive results which may be erroneously used to guide treatment decisions with unintended consequences. These tests are also costly to repeat and may unnecessarily increase the workload of hospital laboratories.

These recommendations however have a number of limitations. Most published papers report results of tests performed on specimens derived from normal plasma which have been spiked in the laboratory with NOACs. While this provides consistency for test specimens to be processed in different laboratories and on different machines as well as reagents, the effects on actual patient specimens are less well characterised in published literature. Secondly, while we have chosen to only include studies that best match the instruments, reagents and test environment in Singapore, there are limitations to the degree of similarity as no 2 laboratories are alike. The replicability of the published test results cannot be absolutely assured in our laboratories. Additionally, there is currently a dearth of local laboratory data on the interference of DOACs with coagulation testing. Lastly, the summary recommendations represent the line of best fit when consolidating information from various papers. There will therefore be outliers who do not conform to our current interpretation of the reported findings in this aspect. Our paper also does not cover the subject of monitoring DOAC levels which has previously been addressed by our group.[41]

Ultimately, the best recommendations on the interpretation of coagulation tests for patients taking DOACs will have to come from each individual laboratory's own validation studies and experience with a cohort of local Singapore patients. Currently, such a tedious and costly exercise is

DABIGATRAN

	Lupus anticoagulant testing			One-stage factor assays	Mixing studies	Thrombophilia screening				Other tests	
ASSAY	Dilute Russell's viper venom time (dRVVT)	PTT-LA	Phospholipid-corrected silica clotting time (Staclot LA)			Antithrombin	Protein S	Protein C	Activated Protein C (APC) Ratio	vWF:Ag, vWF:RCo	Platelet function tests
EFFECT	• Falsely prolonged • dRVVT ratio cutoff exceeded even at sub-therapeutic levels.	• Prolonged. • Phospholipid correction may be incomplete. • May result in false positive LA.		• Falsely reduced • Significant effects on factors II and V at therapeutic levels. • Significant effects on factors VIII, IX, XI and XII at trough levels.	• Incomplete correction • May suggest false presence of factor inhibitor at peak levels.	• Thrombin-based; falsely elevated AT activity in thrombin-based assays • Significant effects at therapeutic levels.	• Functional assay: clot-based; falsely elevated even at sub-therapeutic levels. • Total/free assays: antigen-based; no effect	Chromogenic; not affected.	Falsely elevated beyond trough levels.	Not affected	
RECOMMENDATIONS	Do not test when patient is on drug.			Do not test when patient is on drug. If testing must be done, recommended to do so at trough levels.	If testing must be done, recommended to do so at trough levels.	If testing must be done, recommended to so do at trough levels.	Do not test for clot-based functional Protein S when patient is on drug. May test for Protein S antigen.	May test.	Do not test when patient is on drug.	May test.	

RIVAROXABAN

	Lupus anticoagulant testing			One-stage factor assays	Mixing studies	Thrombophilia screening				Other tests	
ASSAY	Dilute Russell's viper venom time (dRVVT)	PTT-LA	Phospholipid-corrected silica clotting time (Staclot LA)			Antithrombin	Protein S	Protein C	Activated Protein C (APC) Ratio	vWF:Ag, vWF:RCo	Platelet function tests
EFFECT	• Falsely prolonged • dRVVT ratio cutoff exceeded even at sub-therapeutic levels.	Likely not affected.		• Falsely reduced factors II, V, VII and X, but might still be within normal range • Significantly reduce factors VIII and IX at therapeutic levels • Falsely reduced XI and XII levels • Chromogenic assays are also affected	Likely to be incompletely corrected	Thrombin-based; not affected	• Functional assay: clot-based; falsely elevated even at sub-therapeutic levels. • Total/free assays: antigen-based; no effect	Chromogenic; not affected.	Falsely elevated beyond peak levels.	Not affected	
RECOMMENDATIONS	Do not test when patient is on drug.			Do not test factors II, V, VII and X when patient is on drug. If testing for factors VIII, IX, XI and XII must be done, recommended to do so at trough levels.	If testing must be done, recommended to do so at trough levels.	May test.	Do not test for clot-based functional Protein S when patient is on drug. May test for Protein S antigen.	May test.	If testing must be done, recommended to do so at trough levels.	May test.	

APIXABAN

	Lupus anticoagulant testing			One-stage factor assays	Mixing studies	Thrombophilia screen				Others	
ASSAY	Dilute Russell's viper venom time (dRVVT)	PTT-LA	Phospholipid-corrected silica clotting time (Staclot LA)			Antithrombin	Protein S	Protein C	Activated Protein C (APC) Ratio	vWF:Ag, vWF:RCo	Platelet function tests
EFFECT	Falsely prolonged but dRVVT ratio only exceeded cutoff at supra-therapeutic levels.	Likely not affected.		Falsely reduced significant beyond peak levels.	Likely to be incompletely corrected	Thrombin-based; not affected	• Functional assay: clot-based; falsely elevated even at sub-therapeutic levels. • Total/free assays: antigen-based; no effect	Chromogenic; not affected.	Likely to be falsely elevated beyond peak levels.	Not affected	
RECOMMENDATIONS	If testing must be done, recommended to do at trough levels.			If testing must be done, recommended to do so at trough levels.	If testing must be done, recommended to do so at trough levels.	May test.	Do not test for clot-based functional Protein S when patient is on drug. May test for Protein S antigen.	May test.	If testing must be done, recommended to do so at trough levels.	May test.	

Table 3. Effects of NOACs on specialised coagulation testing.
LA: Lupus anticoagulant; PTT: Partial thromboplastin time; vWF: von Willebrand factor

not possible for the majority of busy service laboratories in Singapore. While this current collaborative effort to guide coagulation testing has its limitations, it will go some distance in putting sense to a confusing and relatively new area of testing. Widespread availability of specific tests for measurement of drug levels of the DOACs with rapid turnaround times will eventually resolve the current dilemma confronting our clinicians, especially in emergency situations or whenever the safety and efficacy of the DOACs are in question. Laboratories in Singapore should therefore prioritise the introduction of such tests for improving the care of patients who are taking DOACs. Our workgroup will also need to be mindful of providing updates to this paper when more local data and experiences become available in future. In the interim, this represents our best effort which we hope will benefit clinicians prescribing and managing patients taking DOACs.

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Viva-Asia Blood and Marrow Transplantation Groups – A Survey of Consortium Activity over a 12-year Period (2000 to 2011)

Dear Editor,

Haematopoietic stem cell transplantation (HSCT) is an established treatment for many malignant and non-malignant childhood conditions. Because of regional differences in disease spectrum and donor availability, transplant approaches may vary. The Viva-Asia Blood and Marrow Transplantation (VABMT) Group was established in 2009 to address the specific transplant issues for children that were represented in the transplant centres in the East. Members of this working group perform paediatric HSCTs in 6 Asia Pacific countries, including 3 centres in Singapore, 2 in Hong Kong, 2 in mainland China, 2 in Thailand and 1 each in Malaysia and Philippines.

The volume of HSCT and the trends of transplant care, data on transplantations performed from 2000 to 2011 inclusive were obtained from all 11 centres. Analyses focused on the types of disease, donor, stem cell source, and changes of practice over time. The centres involved were from Singapore (KK Women's and Children's Hospital, National University Hospital, Mount Elizabeth Hospital), Hong Kong (Queen Mary Hospital, Prince of Wales Hospital), mainland China (Shanghai Children's Medical Centre, Nanfang Hospital), Thailand (Ramathibodi Hospital, Siriraj Hospital), Malaysia (Sime Darby Medical Centre) and Philippines (St Luke's Medical Centre).

All 11 centres performed both autologous and allogeneic HSCT. In the 12 years from 2000 to 2011 inclusive, there were a total of 1790 HSCTs performed: 1407 (78.6%) were allogeneic and the remaining 383 (21.4%) were autologous (Table 1). Among the allogeneic HSCTs, 54.9% were for non-malignant conditions and 45.1% for malignant diseases (Table 2). The proportion of HSCTs that were allogeneic increased from 75% in the first 6 years (early cohort) to 80.6% in the second 6 years (recent cohort) (Table 1).

All centres carried out allogeneic HSCTs for both malignant and non-malignant conditions. Overall, there were more transplants performed for non-malignant conditions (54.9%) compared to malignant conditions (45.1%). Acute myeloid leukaemia (AML)/myelodysplastic syndrome (MDS) (40.9%) formed the majority of allogeneic HSCT in malignant conditions (Table 2), followed by acute lymphoblastic leukaemia (ALL) (39.4%), chronic myeloid leukaemia (CML) (12.5%) and others (7.2%). For non-malignant conditions, more than half of the allogeneic HSCT were performed for haemoglobinopathy (62.7%), followed by severe aplastic anaemia (SAA) (17.9%), primary immune deficiency (8.4%), inherited metabolic disease (4.4%) and congenital bone marrow failure (4%).

Unrelated and related donors were almost equally used (Table 3): 48% were unrelated and 52% were related (40.8% were matched sibling/twin and 11.2% were haploidentical). This is consistent with the findings of the Europe Bone Marrow Transplant (EBMT) activity survey[1] in year 2010: unrelated source of stem cells was 53% compared with 41% in related human leukocyte antigen (HLA)-matched sibling source. Unrelated cord blood (CB) and haploidentical donor transplants were increasingly being performed in recent years for patients without a sibling or a matched unrelated donor (Table 3).

For matched-related source of stem cells, the majority (58%) were from bone marrow (BM), while peripheral blood stem cell (PBSC) formed 29.6% of the stem cells source (Table 4). Related CB formed a small percentage (4.4%). For unrelated source of stem cells, 71.1% were from BM or PB while 28.9% were from CB. Notably, the frequency of CB HSCT varied substantially among the 10 centres. For example in Singapore, KK Women's and Children's Hospital and Mt Elizabeth Hospital, and in Hong Kong

Table 1. The Total Number of Allogeneic and Autologous HSCT Performed from 2000 to 2011 among the Asian Centres

	Total	Year		*P* Value	Type of Conditions		*P* Value
		2000 – 2005	2006 – 2011		Malignant	Non-malignant	
Allogeneic HSCT	1407 (78.6%)	475 (75.0%)	932 (80.6%)	0.008	634 (63.5%)	773 (97.7%)	<0.001
Autologous HSCT	383 (21.4%)	158 (25.0%)	225 (19.4%)		365 (36.5%)	18 (2.3%)	
Total	1790 (100%)	633 (100%)	1157 (100%)		999 (100%)	791 (100%)	

HSCT: Haematopoietic stem cell transplantation

Table 2. The Absolute Number of Allogeneic HSCT Performed for Different Malignant and Non-Malignant Conditions

Disease	Total, n (%)	2000 – 2005	2006 – 2011	*P* Value
Malignant	634 (45.1%)	233 (49.1%)	401 (43.0%)	0.036
Non-malignant	773 (54.9%)	242 (50.9%)	531 (57.0%)	
Malignant disease				
Acute myeloid leukaemia	206 (32.5%)	78 (33.5%)	128 (31.4%)	0.008
Acute lymphoblastic leukaemia	250 (39.4%)	101 (43.3%)	149 (36.9%)	
Chronic myeloid leukaemia	79 (12.5%)	35 (15.0%)	44 (11.4%)	
Myelodysplastic syndrome	53 (8.4%)	9 (3.9%)	44 (11.9%)	
Other leukaemia	14 (2.2%)	3 (1.3%)	11 (2.4%)	
Lymphoma	22 (3.5%)	4 (1.7%)	18 (4.6%)	
Solid tumour	10 (1.5%)	3 (1.3%)	7 (1.4%)	
Non-malignant				
Severe anaplastic anaemia	138 (17.9%)	34 (14.0%)	104 (19.6%)	0.74
Paroxysmal nocturnal hemoglobinuria	2 (0.3%)	1 (0.4%)	1 (0.2%)	
Congenital bone marrow failure	31 (4.0%)	13 (5.4%)	18 (3.4%)	
Haemoglobinopathy	485 (62.7%)	155 (64.1%)	330 (62.2%)	
Epstein-Barr virus-related disease	1 (0.1%)	0	1 (0.2%)	
Hemophagocytic lymphohistiocytosis	9 (1.2%)	3 (1.2%)	6 (1.1%)	
Langerhans cell histiocytosis	1 (0.1%)	0	1 (0.2%)	
Autoimmune disease	1 (0.1%)	0	1 (0.2%)	
Metabolic disease	34 (4.4%)	11 (4.6%)	23 (4.4%)	
Primary immune deficiency	65 (8.4%)	23 (9.5%)	42 (7.9%)	
Others	6 (0.8%)	2 (0.8%)	4 (0.8%)	

Prince of Wales Hospital, unrelated CB formed 60 to 80% of unrelated stem cells sources (Table 5). Autologous HSCT accounted for 383 out of 1790 (21.4%) of total number of HSCT. Of these, 93.7% of autologous source of stem cells were peripheral blood stem cell and BM transplants.

Clinical application of allogeneic HSCT has been increasing steadily over the past 12 years as the number of unrelated BM/peripheral blood donors and CB units have become more readily available for public use. The number of allogeneic HSCT has increased significantly by more than 2 folds in our recent cohort than in the earlier cohort (Table 1). In the recent cohort, we found an increase in number of HSCT for non-malignant condition in almost all categories (Table 2). For SAA and haemaglobinopathy, the 2 most common types of non-malignant conditions, the number of HSCT had risen significantly from 34 to 104 cases for SAA and from 155 to 330 cases for haemoglobinopathy comparing the 2 cohorts.

Over the period, there was a significant change in donor source for allogeneic HSCT (Table 3). In the earlier period (2000 to 2005), 51.6% of allogeneic HSCTs were matched sibling/twin donor while unrelated adult donor/CB formed 36.8% of allogeneic HSCTs. In the recent period, unrelated adult donor/CB accounted for 53.6% of allogeneic HSCTs. This was made possible with the expansion of national and international marrow registries and public CB banks. Unrelated adult donor HSCTs increased from 119 to 361 while unrelated cord from 56 to 139 (P <0.001). The

Table 3. The Donor Sources for Allogeneic HSCT

Year	Total	Related 732 (52%)		Unrelated 675 (48%)		*P* Value
		Matched Sibling/Twin	Haplo-identical	Adult Donor	Cord Blood	
2000 – 2005	475	245 (51.6%)	55 (11.6%)	119 (25.0%)	56 (11.8%)	<0.001
2006 – 2011	932	329 (35.3%)	103 (11.1%)	361 (38.7%)	139 (14.9%)	
Total	1407	574 (40.8%)	158 (11.2%)	480 (34.1%)	195 (13.9%)	

Table 4. The Sources of Stem Cells from Matched-Related or Unrelated Donor

	Total, n (%)	2000 – 2005	2006 – 2011	*P* Value
MSD/Twin				
Bone Marrow	333 (58.0%)	143 (58.4%)	190 (57.8%)	<0.001
Peripheral Blood	170 (29.6%)	76 (31.0%)	94 (28.6%)	
Cord Blood	25 (4.4%)	17 (6.9%)	8 (2.4%)	
Others (combination)	46 (8.0%)	9 (3.7%)	37 (11.2%)	
Total	574 (100%)	245 (100%)	329 (100%)	
Unrelated Donor				
BM	181 (26.8%)	81 (46.3%)	100 (20.0%)	<0.001
PB	299 (44.3%)	38 (21.7%)	261 (52.2%)	
CB	195 (28.9%)	56 (32.0%)	139 (27.8%)	
Total	675 (100%)	175 (100%)	500 (100%)	

unrelated cord forms a small but significant source of unrelated stem cells from 11.8% to 14.9% over 2 periods among the Asia Pacific HSCT centres.

In matched-related donor HSCT, peripheral blood stem cell is a good alternative source, especially if there is a considerable discrepancy in body weight between the donor and recipient. The majority source of stem cells (58%) was from BM in a related setting. For unrelated adult donor, the source was usually peripheral blood which formed 44.3%. We saw a change in the proportion of peripheral blood from 21.7% to 52.2% (P <0.001) during the period of 2006 to 2011 inclusive. Related CB represented a small percentage but constituted an important source of stem cells, as the medical condition of the recipient may not allow time for the donor to grow up to be a marrow or peripheral blood stem cells donor.

In Japan, 60% of unrelated source of stem cells were from BM/PB and 40% were from CB.[2] Unrelated donors in Asia were relatively difficult to find because ethnic Asians are under-represented in most major international registries such as National Marrow Donor Program (NMDP) in the United States.[3] In recent years, The China Marrow Donor Program, with about1 million potential donors, opened its doors to international usage in 2012.[4] Before that, Asian Oriental recipients, especially ethnic Chinese, had to depend mainly on Buddhist Tzu Chi Stem Cell Centre in Taiwan. It was established in 1994 and has been one of the largest source of unrelated stem cells for Oriental recipients.[5]

Thirty-nine percent of unrelated HSCT were from CB (Table 3), a growing source of stem cells in this part of world with multiracial and multiethnic populations, especially in countries like Malaysia and Singapore. In the Asia Pacific

Table 5. The Sources of Stem Cells for Unrelated HSCT from Different Centres

Centres	Peripheral Blood/Bone Marrow	Cord	Total
China: Nanfang	150	4	154
China: Shanghai Children Medical Centre	136	30	166
Hong Kong: Prince of Wales Hospital	35	55	90
Hong Kong: Queen Mary Hospital	39	35	74
Malaysia: Sime Darby Medical Centre	11	10	21
Philippines: St. Luke Medical Centre	1	1	2
Singapore: Women's and Children's Hospital	8	27	35
Singapore: National University Hospital	37	23	60
Singapore: Mt. Elizabeth Hospital	3	7	10
Thailand: Siriraj	15	0	15
Thailand: Ramathibodi Hospital Mahidol University	45	3	48
Total	480 (71.1%)	195 (28.9%)	675

Bone Marrow Transplant (APBMT) survey in 2008, unrelated CB contributed 30 to 80% of unrelated HSCT in several centres, both for children and adult unrelated HSCT (unpublished data: Lila M, Atsuta Y, Hyo R, et al. APBMT annual report. Monograph 2010; v4).

In conclusion, the Viva-Asia HSCT Consortium gives us the opportunity to understand the different pattern of HSCT in Asia in terms of types of HSCT, choice of stem cells and indications for HSCT. Some of these patterns are unique to Asia. Continuing collaboration among centres in Asia will allow us to improve the outcomes of allogeneic HSCT for different diseases, as surveys form the backbone and pave the way for further collaborative studies and researches. In conclusion, the limitation of this study is that not all paediatric centres of the mentioned countries were surveyed.

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Peripheral Osteoma of Palate

Dear Editor,

Osteoma was described as a specific entity by Jaffe in 1935 and since then, hundreds of cases have been published which bear out his original criteria stating that there is little evidence to suggest that the lesion, being a benign neoplasm which formed large amounts of osteoid later getting calcified, was a result of an inflammatory process.[1]

Shafer et al in 1983 described osteomas as a benign neoplasm characterised by the proliferation of compact or cancellous bone, usually in an endosteal or periosteal location, and rarely entirely in soft tissues.[2]

The exact aetiology and pathogenesis of peripheral osteoma is unknown. Both hamartomatous and neoplastic factors have been advocated with no definite conclusion.[3] We report a case of peripheral osteoma in the palate of a 48-year-old female patient. To the best of our knowledge, this is only the second reported case of palatal peripheral osteoma.

Case Report

A 48-year-old female patient presented to our department with a chief complaint of palatal swelling which was slow in growth, painless, and was present from the last 8 months. On oral examination, a firm, lobulated, well circumscribed, and exophytic mass of 1.5 cm × 2 cm in diameter was found on the maxillary posterior right palatal area. Intra-oral periapical radiograph revealed a patchy radiopacity (Fig. 1).

Surgical excision of the lesion was done under local anaesthesia and excised tissue was sent to the oral and maxillofacial pathology department (Fig. 2).

Histopathological examination revealed parakeratinised stratified squamous epithelium. The subepithelial core of connective tissue was made up of collagen fibres and fibroblasts (Fig. 3). The deeper connective tissue showed a capsule of bone surrounding the adipose tissue (Fig. 4). Osteocytes were also observed within the trabeculae (Fig. 5). After the correlation of all the clinical and histopathological features, we reached the final diagnosis of peripheral osteoma.

Discussion

Peripheral osteomas are normally an incidental finding since they are asymptomatic but depending on the location and the size of the lesion, they can cause facial deformity.[4] Osteomas can occur at any age but are found most frequently in young adults. Osteomas in the maxillofacial region have been reported in patients between the ages of 29.4 and 40.5 years. Osteomas usually remain less than 2 cm in size after years of slow enlargement.[5]

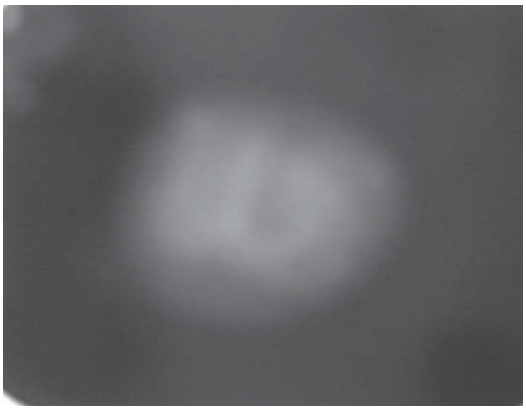

Fig. 1. Patchy radiopacity seen in radiograph.

Fig. 2. Excised specimen sent for histopathological examination.

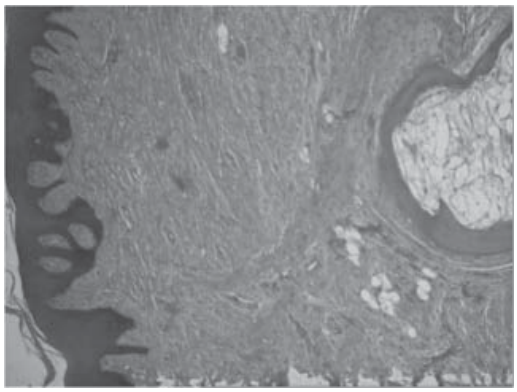

Fig. 3. Parakeratinised stratified squamous epithelium and connective tissue (haematoxylin and eosin (H & E) stain 10 X).

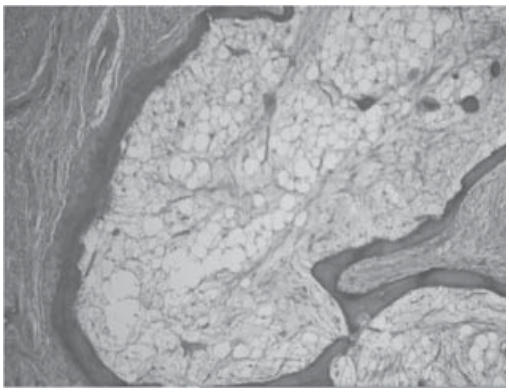

Fig. 4. Thin core of cancelous bone surrounded the adipose tissue (haematoxylin and eosin (H & E) stain 10X).

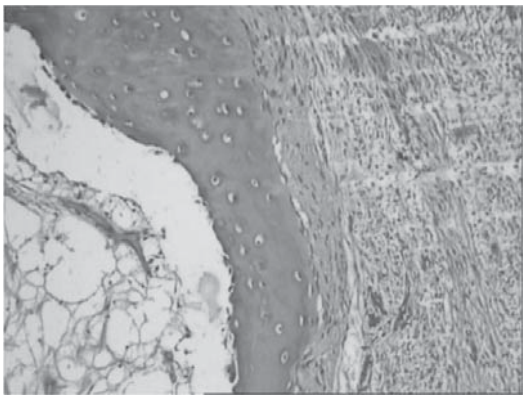

Fig. 5. High power view showing osteocytes within the bone and adipose tissue (haematoxylin and eosin (H & E) stain 10X).

Osteomas can be classified as being solitary or multiple; the latter are mainly associated with Gardener's syndrome.[6] Gardener syndrome is a rare autosomal dominant genetic disorder characterised by multiple colorectal adenomatous polyps and extraintestinal lesions such as multiple osteomas, multiple impacted teeth, multiple odontomas and mesenchymal tumours of skin and soft tissue.[7]

Osteomas are more frequent in males than in females by approximately 2:1.[2] Extragnathic osteomas are more commonly found in the cortical plate of long bones such as the femur and the tibia.[4] In the maxillofacial region, osteomas occur most frequently in the sinuses. The most common site is the frontal sinus, followed by ethmoidal and maxillary sinuses.[1-3] Other locations include the external auditory canal, orbit and temporal bones, and pterygoid plates.[3] With regard to facial bones, osteomas are more common in the mandible than in the maxilla and lingual surface of the mandibular body posterior to premolars and the lower border in the angle region.[1] The palate is a very unusual site for osteomas. We had gone through the PubMed literature and could find only a single case report.[8] Conventional radiological examinations are generally sufficient to diagnose an osteoma. Radiographically, it appears as a unilateral, pedunculated, well-defined, oval or round mushroom-like radiopaque mass with similar density to normal bones.[5] Histologically, osteoma consists of mature, lamellar bone with minimal marrow tissue (compact osteoma) or of trabeculae of mature lamellar bone with intervening fatty or fibrous marrow (cancellous osteoma). There are no reports of malignant transformation of peripheral osteoma. Asymptomatic lesions are left untreated and regular follow-up is done. Surgery is indicated when there are symptoms, deformity, or if the lesion presents active growth. Recurrence is extremely rare.[2]

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Icteric Intraductal Hepatocellular Carcinoma and Bile Duct Thrombus Masquerading as Hilar Cholangiocarcinoma

Dear Editor,

Obstructive jaundice is a rare presenting clinical feature in patients with hepatocellular carcinoma (HCC). Icteric HCC is otherwise known as icteric-type hepatoma.[1] It is known that intraluminal biliary obstruction may occur by one of 3 mechanisms: haemobilia caused by bleeding from the tumour, migration of tumour debris that has separated from the primary growth, or continuous retrograde tumour growth along the biliary tree. Although, HCC with bile duct thrombus (BDT) was historically associated with a poorer prognosis, some studies have shown that adequate surgical resection can still provide sufficient palliation and occasional cure.[2,3]

In the past decade, several groups have reported their experience of HCC with BDT and most of these reports described patients with a significantly sized parenchymal lesion.[4,5] However, a subtype of intraductal hepatocellular carcinoma (IHCC) with BDT without an obvious parenchymal lesion is rarely reported as these predominantly intraductal lesions are often preoperatively misdiagnosed as cholangiocarcinoma.[6-8]

In this report, we present a series of 4 patients with icteric IHCC with BDT without apparent parenchymal lesion. We discuss the clinico-pathological characteristics of this unique subtype of IHCC with BDT and describe the surgical approach to these lesions.

Results

Patients' clinical and tumour characteristics and surgical details are summarised in Tables 1 and 2. One patient with a history of previously resected HCC had a preoperative diagnosis of IHCC with BDT. The other 3 patients were diagnosed preoperatively to have hilar cholangiocarcinomas. All 3 patients with primary presentation of disease had elevated mean CA 19-9 at 1356 μmol/L. The hepatitis B surface antigen (HBsAg) assay was positive in all 4 cases, and the mean alpha-fetoprotein (AFP) assay was 6.03 UG/L. The mean bilirubin level was 136 μmol/L.

Table 1. Characteristics of Presentation, Tumour location, Surgical Intervention and Reconstruction of Patients with Icteric HCC and BDT

Case No.	Age/ Gender	Presentation Preoperative Diagnosis	Location of Intraductal Tumour	Preoperative Biliary Drainage	Surgical Intervention	Biliary Reconstruction
1	63 years/ male	Recurrent/ intraductal HCC	Right main duct and sectorial ducts extending to the confluence, length 5 cm	Nil	Right hemihepatectomy and left main duct margin and tumour thrombectomy	Nil
2	69 years/ male	Primary/hilar cholangiocarcinoma	Right ant sectorial to right main duct extending to the left main duct, length 4 cm	Nil	Extended right hepatectomy, caudate lobe resection, radical resection of bile duct	Left main hepatic duct to jejunum
3	67 years/ male	Primary/ hilar cholangiocarcinoma	Left lateral sectorial to left main to confluence and extending to the right main duct, length 5.5 cm	Nil	Left hemihepatectomy, caudate lobe resection and right and common hepatic duct and radical resection of the bile duct	Right main hepatic duct to jejunum
4	58 years/ male	Primary/ hilar cholangiocarcinoma	Left main duct and sectorial ducts extending to the hilum and involving the distal right main duct, CBD up to cystic duct confluence, Length 6.5 cm	Right PTBD	Extended left hepatectomy, caudate lobe resection and radical resection of the bile duct, right hepatic duct and tumour thrombectomy	Right sectorial ducts cloacalised and anastomosed to jejunal limb

BDT: Bile duct thrombus; CBD: Common bile duct; HCC: Hepatocellular carcinoma; PTBD: Percutaneous transhepatic biliary drainage

Table 2. Clinical and Biochemical Profile of Patients with Intraductal Hepatocellular Carcinoma

Case No.	Chronic Hepatitis	Cirrhosis (Childs Status)	Comorbidities	Albumin	Bilirubin	ALP	ALT	AST	GGT	AFP	CA 19-9	CEA
1	B	Nil	Hypertension	34	153	162	89	62	362	1.9	Nil	Nil
2	B	A	Hypertension, diabetes mellitus	34	141	258	203	145	229	10.7	467	2.8
3	B/Chronic alcoholism	B	Nil	33	201	330	154	110	1091	5.3	2213	2.2
4	B	B	Nil	36	49	231	79	73	413	6.2	1388	Nil

AFP: Alpha fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CA 19-9: Cancer antigen 19-9; CEA: Carcinoembryonic antigen; GGT: Gamma-glutamyl transpeptidase

All patients were operated on within 1 week of diagnosis. One patient underwent preoperative percutaneous drainage at another institution for treatment of cholangitis. The surgical procedure was determined based on the preoperative determination of the location of the primary tumour and the tumour/tumour thrombus extension in the biliary system, the precise operative exploration results, or both. All 4 patients had Satoh type II BDT (Fig. 1).[5]

The patient with the preoperatively diagnosed recurrent IHCC underwent a hemihepatectomy with removal of the ipsilateral bile duct and tumour thrombectomy via the transected end of the bile duct. On histological examination, there was a small 2 mm focus of parenchymal tumour close to the main bile duct, the thrombus which extended distally had no significant attachments to the lumen of the common hepatic duct (CHD) (Figs. 2 and 3).

In the other 3 patients with preoperative diagnosis of hilar cholangiocarcinoma, major hepatic resection of the dominant side of the tumour, caudate lobectomy, and radical resection of the bile duct was performed. Histological examination showed that the IHCC were found to invade the main bile duct and extend 1 cm to 2 cm radially into the hepatic parenchyma in all 3 cases. The BDT extended distally into the CHD, but did not show significant thrombus attachments to the CHD and consisted mainly of inspissated bile. Notably, all 3 patients had evidence of microvascular invasion and 2 had associated portal vein invasion (Table 3).

The patients were all discharged within 2 weeks of hospitalisation and had no major complications necessitating further procedures. Two patients developed recurrent tumours at 7 and 24 months and passed away at 9 and 50 months, respectively. Two patients were disease-free at 16 and 29 months to date (Table 4).

Discussion

Jaundice in HCC usually occurs in advanced liver cirrhosis, caused by tumour mass effect compressing

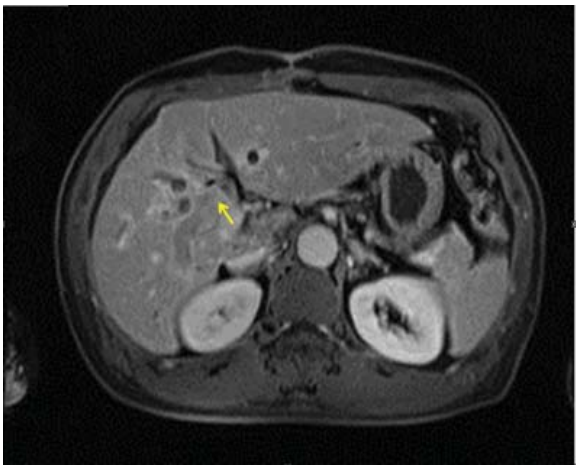

Fig. 1. A CT scan of a patient with intrahepatic bile duct thrombus. Arrow points to the thrombus.

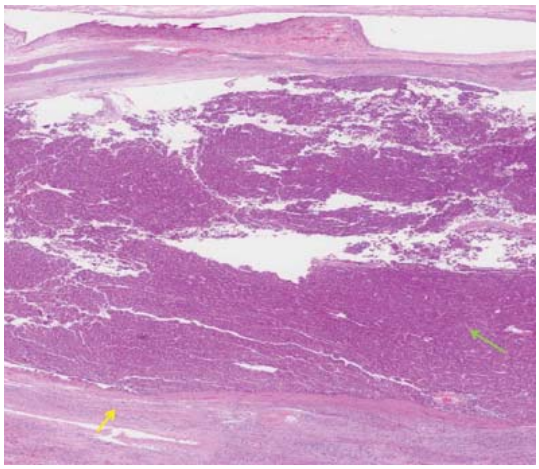

Fig. 2. Histological slide of intrahepatic bile duct thrombus. Long arrow points to the tumour thrombus and the short arrow points to the bile duct wall.

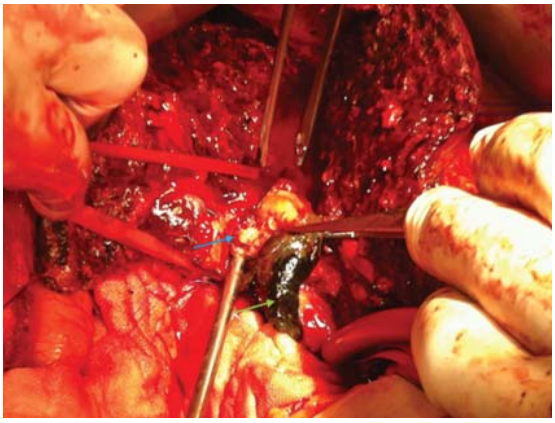

Fig. 3. Intraoperative picture of intrahepatic bile duct thrombus. Upper arrow points to the tumour thrombus, lower arrow points to the inspissated bile thrombus that is removed easily.

on bile ducts or massive tumour infiltration of the liver parenchyma.[9,10] Jaundice caused by BDT is a rare obstructive variant, being identified in only 1% to 13% of patients treated operatively.[3,11,12] Satoh et al classified the subtypes of HCC with BDT according to the level of BDT.[5] However, IHCC with BDT with no apparent parenchymal lesion was not well described within the larger series.[4-6] In this report, we point out the important pathological differences which significantly impact the surgical approach.

The low rate of surgical resection of patients with HCC and BDT is due to liver impairment secondary to liver cirrhosis exacerbated by obstructive jaundice.[13] Thus, an attractive treatment option for HCC is the removal of the bile duct thrombus without en bloc resection of the involved bile duct and liver parenchyma, although some authors hypothesised that tumour thrombectomy through a choledochotomy might cause peritoneal dissemination and local recurrence at the site of choledochotomy due to intraoperative implantation.[14] Satoh et al and Shiomi et al showed that there were no significant differences in the survival of patients who underwent thrombectomy of the BDT compared with those who underwent bile duct resection, provided that there was no invasion of the bile duct.[4,5] Narita et al also reported that bile duct tumour thrombi were only attached to the mucosa of the bile duct by a thin stalk without invasion into the submucosa.[15] This leads to the suggestion of curative tumour thrombectomy without a need for extended liver resection as a viable option of treatment for HCC with BDT.

However, in 3 of our cases with IHCC and BDT, the pathological specimens showed that the main bile ducts at the epicentre of the tumour were extensively involved with surrounding parenchymal involvement such that resection of the bile ducts and its associated liver segments were necessary to remove the tumour en bloc instead of a simple tumour thrombectomy. This was in contradistinction to the pathological findings from all the reported series of HCC with BDT that main bile duct invasion was not seen in the reported cases.[4,5,8] This finding is significant as it mandates surgical resection of the hepatic parenchyma surrounding the intraductal HCC in this subtype of IHCC.

In our cases, when the main tumour lesion was resected, the residual BDT which extends distally into the common

Table 3. Pathological Characteristics of the Intraductal Hepatocellular Carcinoma and Bile Duct Thrombus

Case No.	Edmonson Grade	Tumour Capsule/ Size of Intraductal Tumour	Margins (mm)	Intrahepatic Main Bile Duct Invasion	Bile Duct Thrombus	Portal Vein Invasion	Lymph Node Involvement	Micro Vascular Invasion
1	Moderate	NA/ 2 mm, focal involvement of the parenchyma	20	No	Extending distally into the CHD and consists of inspissated bile only	No	NA	No
2	High	Incomplete/ invading radially into the bile ducts and 1 cm into the parenchyma	15	Yes	Extending distally into the CHD and mainly inspissated bile	No	No	Yes
3	Moderate	Incomplete/ invading radially into the bile ducts and 2 cm into the parenchyma	1	Yes	Extending distally into the CHD and mainly inspissated bile	Yes	No	Yes
4	High	Incomplete/ invading radially into the bile ducts and 2 cm into the parenchyma	10	Yes	Extending distally into the CHD and mainly inspissated bile	Yes	No	Yes

CHD: Common hepatic duct; NA: Not applicable

Table 4. Postoperative Outcomes and Long Term Follow-up Results

Case No.	Complications	DFS/Months	Recurrence	Adjuvant Therapy	OS/Months
1	Nil/discharged POD 10	16	Nil	Nil	16
2	Nil/discharged POD 10	7	Recurrent at Segment 4	Nil	9
3	Nil/discharged POD 9	24	Recurrent at Segment 6	TACE X1 cycle	50
4	Nil/discharged POD 8	29	Nil	Nil	29

DFS: Disease-free survival; OS: Overall survival; POD: Postoperative day; TACE: Transarterial chemoembolisation

hepatic duct consisted mainly of inspissated bile and were easily removed via thrombectomy with no attachment to the bile duct. This suggests that the observations of the previous studies held true for thrombi which were extending far away from the epicentre of the tumour.[4,5,8] For certainty of the oncologic clearance, resection of the parenchyma around the epicentre of the tumour thrombus, usually in the main bile ducts, is recommended for IHCC based on our experience.

Conclusion

Icteric IHCC with BDT are a rare subtype of HCC and are associated with main bile duct invasion and parenchyma involvement around the epicentre of the IHCC. We advocate parenchyma resection around the IHCC in the main duct. The distally extending BDT are often not attached to the bile ducts and can be safely removed via thrombectomy.

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Fever in a Patient with a Previous Gastrectomy

A 64-year-old male retiree developed fever, vomiting and lethargy over 1 day. He had a significant past history of gastric adenocarcinoma (stage T3N0) and underwent a laparoscopic proximal gastrectomy with intracorporeal anastomosis 1 year ago, followed by adjuvant chemotherapy. In addition, he had Child's B liver cirrhosis complicated by oesophageal varices which were ligated. On presentation to the emergency department, he had a low grade fever of 37.9°C and was hypotensive with a blood pressure of 70/40 mmHg. Heart rate was 78 beats per minute, respiratory rate was 17 breaths per minute, and oxygen saturation was 98% on room air. He had distended neck veins, muffled heart sounds, and pulsus paradoxus. Abdominal examination was unremarkable.

Electrocardiogram (ECG) documented low electrical voltages with >1mm saddle-shaped ST-segment elevations in multiple leads (Fig. 1). Bedside echocardiography confirmed a large pericardial effusion with tamponade physiology. On the full blood count, the white cell count was elevated at 14 x 10^9/L with predominance of neutrophils (92%), and C-reactive protein was elevated at 68 mg/L.

In view of persistent hypotension despite multiple fluid boluses, intravenous dopamine was initiated, followed by an urgent pericardiocentesis in the coronary care unit. We aspirated a total of 300 mL of foul-smelling purulent pericardial fluid.

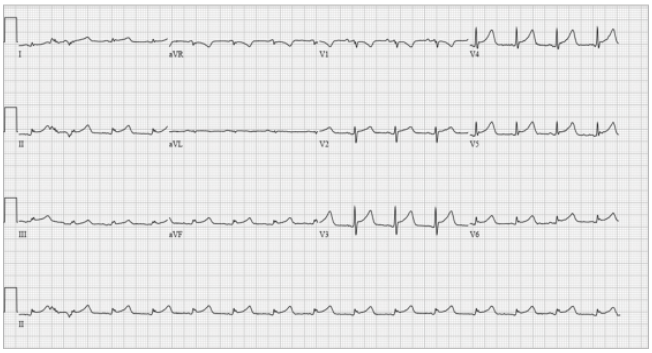

Fig. 1. Electrocardiogram (ECG) performed in the emergency department showing a combination of saddle-shaped ST-segment elevations in the precordial and limb leads, as well as small QRS complexes globally. There is no electrical alternans.

We made the primary diagnosis of purulent pericarditis causing cardiac tamponade. Intravenous (IV) ceftriaxone was started empirically. After pericardial drainage, transthoracic echocardiography (Fig. 2) showed a normal ejection fraction of 60%, and a small to moderate residual pericardial effusion containing echogenic material.

Analysis of the pericardial fluid revealed an exudative picture: fluid glucose was low at <1.1 g/mmol; fluid protein to serum protein ratio was >0.5. Nucleated cell count was high at 50190/μL, with 96% neutrophils. Gram stain smear showed gram-positive cocci, and occasional gram-negative rods and yeast cells. Acid-fast bacillus stain was negative. Pericardial fluid culture grew multiple micro-organisms which included: a) Methicillin-sensitive *Staphylococcus aureus*, sensitive to cloxacillin; b) *Viridans streptococci*, sensitive to penicillin; c) *Haemophilus parahaemolyticus*, sensitive to amoxicillin/clavulanate; and d) *Candida albicans* – sensitive to fluconazole.

The antimicrobial therapy was thus escalated to a broad-spectrum combination of IV amoxicillin/clavulanate 1.2 g 6-hourly, IV ceftazidime 2 g 8-hourly, and IV fluconazole 200 mg 12-hourly.

The pericardial cytology obtained was highly unusual, demonstrating the presence of squamous cells normally found in the upper oesophagus.

A computed tomography (CT) scan of the thorax was obtained (Fig. 3). It showed non-specific oesophageal thickening, a fluid-filled and distended oesophagus, and a large complicated pericardial effusion with pneumopericardium.

What is/are the most likely underlying cause(s) of purulent pericarditis in this patient?

A. Recurrence of gastric carcinoma causing a fistula
B. Oesophago-pericardial fistula as a complication of proximal gastrectomy
C. Infective endocarditis
D. Biliary tract infection
E. Myocardial abscess

Answer: A or B

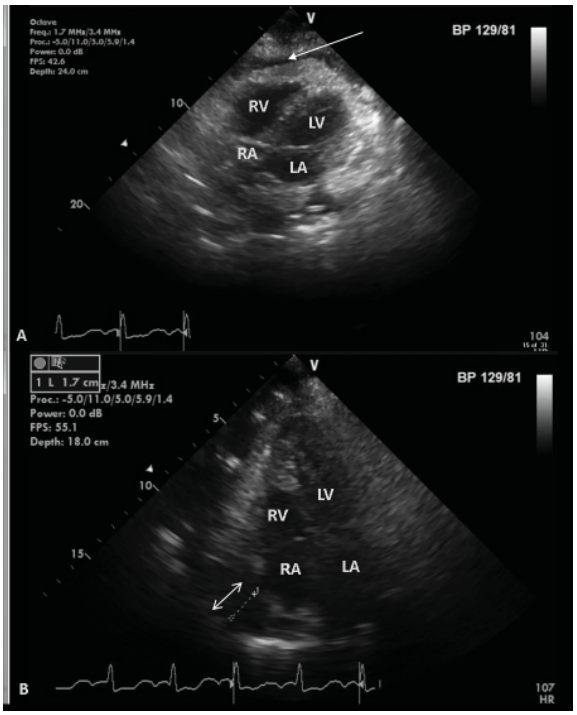

Fig. 2. A) shows the post-pericardiocentesis transthoracic echocardiography with modified apical 4-chamber view. Arrow points to fibrinous deposits within the pericardium, and a small echo-free space anterior to the heart. At B), the transthoracic echocardiography with apical 4-chamber view is shown. Arrow points to small to moderate echo-free space lateral to the right atrium. The pericardium appears irregular due to fibrin deposits.

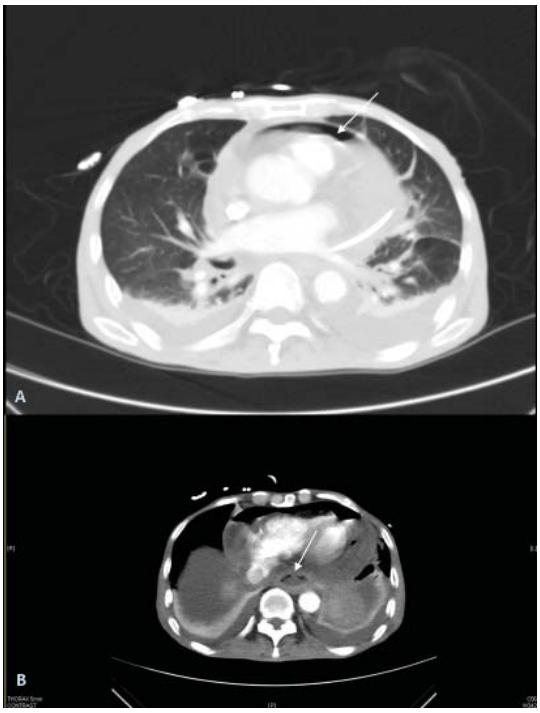

Fig. 3. A) presents the CT thorax (lung window) post-pericardiocentesis showing pneumopericardium (arrow) and a large pericardial effusion with heterogeneously dense appearance, suggesting a complicated effusion. B) presents the CT thorax (abdominal window) showing a fluid-filled oesophagus (arrow) with non-specific thickening without features suggesting possible abscess.

The upper gastrointestinal surgery team was consulted and the plan was for an oesophagogastroduodenoscopy when the patient was more stable.

Unfortunately, the patient developed progressive septic shock and disseminated intravascular coagulation not responding to supportive therapy. He demised 5 days into admission. The coroner's report concluded septicaemia with multi-organ failure due to infective pericarditis, on a background history of gastric adenocarcinoma. No postmortem was performed.

Discussion

Purulent pericarditis is defined as a localised infection of the pericardial space with gross pus in the pericardium, or microscopic purulence with more than 20 leukocytes per high power field. Although rare, mortality rates can reach 40% in treated patients.[1]

Common predisposing factors, present in our patient, include chronic alcohol abuse, immunosuppression and malignancy.[1,2] Less than a quarter of cases are attributable to a primary infectious focus, such as pneumonia.[2]

There are 5 main modes of spread of infection to the pericardial space; most commonly contiguous spread from an intrathoracic focus. Other modes of spread include hematogenous, pericardial perforation from injury/surgery, extension from the myocardium, and subdiaphragmatic extension. In our patient, the likely mode of spread is contiguous; either from partial breakdown of surgical gastro-oesophageal anastomosis causing fistulation into the pericardium, or recurrence of the carcinoma invading into the pericardium.

All 4 micro-organisms isolated from our patient's pericardial fluid are common flora of the mouth and nasopharynx. *Staphylococcus aureus* is most common, with up to 36% of cases over a period of 60 years.[3,4] *Viridans streptococcal* pericarditis may present subacutely, and may originate from mediastinitis caused by oesophageal perforation, thoracic surgery or pneumonia. *Hemophilus parahaemolyticus* is a gram-negative commensal of the nasopharynx. It may cause serious infections such as aspiration pneumonia, but had not previously been described in purulent pericarditis. *Candida* species causing purulent pericarditis are often fatal, especially in immunocompromised and those with previous oesophagogastrectomy.[5]

Typical symptoms of purulent pericarditis include high fever, tachycardia, cough, and chest pain. However,

presentation may be atypical, such as that in our patient (low grade fever and lethargy).

ECG features include those of acute pericarditis, such as diffuse ST-segment elevation (present in our patient), as well as PR-segment depression in the first 2 weeks. This is followed by normalisation of these segments within 3 weeks, then widespread T-wave inversions and subsequent normalisation. If a large pericardial effusion is present, QRS complexes appear small with voltages of less than 0.5 mV in the limb leads and less than 1 mV in the precordial leads. Electrical alternans may be noted in large effusions. Transthoracic echocardiography will determine the size of the pericardial effusion, but cannot distinguish between purulent collections and sterile inflammatory effusions.

The diagnosis is established by echocardiography-guided pericardiocentesis, yielding a sample with high protein, glucose less than 2 mmol/L, and leukocyte count of 6000 to 240,000 cells/μmol.

Immediate management requires urgent pericardial drainage. Pericardiocentesis with percutaneous catheter drainage is quickest; however thick pericardial fluid may loculate, resulting in constrictive pericarditis. Surgical options include pericardiotomy (pericardial "window") or pericardiectomy (removal of the pericardium). Intrapericardial fibrinolysis is an alternative to surgery, but pericardiectomy is indicated if there is failure of complete drainage despite repeated fibrinolysis attempts.[6]

Initial empiric antibiotic therapy should target *Staphylococcus aureus*, especially in the immunocompromised, with some experts proposing vancomycin, targeting methicillin-resistant *Staphylococcus aureus* (MRSA). Anaerobes and gram-negative bacteria should be targeted if a gastrointestinal origin is suspect. Empiric antibiotic regimens include vancomycin + ceftriaxone, imipenem, piperacillin/tazobactam, or cefepime. Empiric IV fluconazole is usually added in the severely immunocompromised or those with recent intensive care unit (ICU) stay. Further antibiotic adjustments should be guided by pericardial culture. Antibiotic therapy is recommended for 3 to 6 weeks depending on fever resolution and normalisation of white cell count.

Long-term complications include constrictive pericarditis and persistent purulent pericarditis. Pericardiectomy at this stage is difficult due to multiple adherences.

Oesophago-pericardial fistula is very rare, with fatality up to 76% in the first month.[7] Most fistulae are from benign oesophageal disease, with a quarter of cases from oesophageal malignancies.[8] Benign oesophageal causes include ulcers, foreign body perforation, and iatrogenic surgical site breakdown. Clinical symptoms include fever, dyspnoea and retrosternal pain. A systolic "waterwheel" murmur may be heard if pyopneumopericardium develops.[9,10]

Pneumopericardium is the most common radiologic finding in an oesophago-pericardial fistula, apparent in our patient. An oesophago-pericardial fistula is best demonstrated by oesophagogastroscopy. Administering oral gastrograffin may demonstrate filling of the pericardial sac through the fistula. This is done after adequate pericardial fluid drainage, to prevent cardiac tamponade.[10] CT may also demonstrate gastrograffin in the pericardial space.

We strongly suspected an oesophago-pericardial fistula in our patient because of upper oesophageal pathogens on pericardial fluid culture, and squamous cells on cytology. As he was drowsy, administering gastrograffin would pose an unacceptably high aspiration risk.

Little has been described about treating an oesophago-pericardial fistula. Strategies involve early diagnosis, pericardial drainage, and targeted anti-microbial therapy, then early operative closure of the fistula. Endoscopic stenting may temporarily seal off the fistula before definitive surgery. A recent case report described management of Barrett's oesophago-pericardial fistula, with temporary esophageal stenting, closing of the fistula with an autologous pericardial patch and a feeding jejunostomy.[11]

Conclusion

Clinicians should be aware of the potentially fatal condition of purulent pericarditis. Early diagnosis and drainage is critical. Oesophago-pericardial fistula as the cause should be suspected in a patient with a history of upper gastrointestinal carcinoma and ECG changes of pericarditis.

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