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"A man is but the product of his thoughts; what he thinks, he becomes."

Gandhi (1869 – 1948)
Indian leader

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Editorial

Pathway to Hepatitis Elimination and Control

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It has been 8 years since the World Health Assembly passed a resolution that viral hepatitis is indeed a major public health threat. Already, the World Health Organization (WHO) has set ambitious targets for 2030 to reduce new viral infections by 90%, diagnose 90% of infections and have 80% of eligible patients treated. For hepatitis C (HCV), as highly effective therapies to cure almost 100% of cases with 3 months of oral therapy have been achieved, the strategy has shifted to public health, resource allocation and utilisation, and policy and implementation.

In Singapore, formulation of a national strategy is slowly taking place, with a possible micro-elimination approach. However, the infrastructure to identify and deliver therapy needs to be put in place. For hepatitis B (HBV), while excellent agents to control the disease are available, the goal of functional cure—defined as loss of hepatitis B surface antigen (HBsAg) 6 months after stopping therapy—has yet to be achieved in significant numbers of patients. Efforts to address this requires understanding the pathogenesis of chronic hepatitis B (CHB) clearance—a key goal of the 'Hepatitis B Translational Clinical Grant'—as well as identification of new targets and agents that are likely to lead to a functional cure. Thirty-six agents encompassing 10 classes of compounds are in preclinical and clinical testing, making this likely in the near future.

It is timely to see how far we have come, and how far we still have to go to address the spectre of viral hepatitis. It is a leading cause of mortality in the Asia Pacific and is estimated to cause over 1 million deaths per year according to the Global Health Survey[1] (the vast majority due to chronic CHB and the remainder due to chronic hepatitis C [CHC]). In Singapore, the impact of viral hepatitis is relatively smaller, in large part due to the foresight of early implementation of the HBV vaccination programme,[2] a strategy that has led to a considerable reduction in CHB. The overall prevalence of CHB was reduced to 3.6%[2] in 2010, from 5% to 6% in the 1980s.[3] However, HBV-related liver disease is still a substantial problem.[4] Hence, there should be no room for complacency as the patients who develop these complications are generally above 50 years of age, while the oldest vaccinees are in their mid-20s. Does this mean that we have to wait another 2 to 3 decades before the benefits of vaccination are realised? Certainly not since much can be done to address the issue. First, however, we should take a page from the war against CHC to determine the strategic direction for CHB. HCV differs from HBV in that the virus is entirely cytoplasmic in its replication cycle,[5] and has no nuclear lifecycle,[6] nor does it integrate into the host genome.[7] In the decade of 2000 to 2010, the standard of care was interferon therapy, with the addition of ribavirin and pegylation of interferon; treatment of HCV could be optimised no further with SVR rates of 40% to 70% at the cost of toxicity of antiviral therapy.[8] Nonetheless, these SVR rates comprise a cure of HCV and are rates well above that achieved for HBV with existing therapies today. The eradication of HCV at that time was not even a consideration and many patients who were treatment failures or ineligible for therapy had no possibility of cure and either perished from advanced liver disease or liver cancer, with only a few fortunate patients being transplanted. With the advent of continually improving oral direct acting antiviral (DAA) therapy, we now have approved pan-genotypic oral DAA therapy with SVR rates close to 100%, representing an easy, safe cure strategy.[9,10] At this time, we can contemplate HCV eradication—the WHO has set optimistic goals and timelines to achieve this.[11] This is a remarkable development for a condition that was unrecognised by the WHO only 8 years ago.[12]

Now, the war has moved to a different stage as the search for a cure is over. In a sense, the easy work has been done, and the search for HCV-positive patients takes on public health, financial, socioeconomic, policy and political overtones.[13] The WHO has set the template, but each country has to make its own decisions on whether, and how to implement. For Singapore, the challenges are more straightforward since the prevalence rate is extremely low (approximately 0.1%)[14] and likely to be archived in well characterised risk groups such as renal dialysis patients, blood transfusion

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recipients, people who inject drugs and migrants from countries that harbour high rates of HCV. Once HCV-infected patients in these risk groups are identified, they can be progressively treated and cured (a strategy called micro-elimination).[15] In Singapore, the low burden of disease is counterbalanced by the high cost of treatment, but the consequences of non-treatment may be even higher in increased morbidity and mortality and the even higher cost of managing complications.[16] Notwithstanding the policy issues, there are infrastructure needs that can streamline the path to elimination. The WHO defines elimination as the complete cure of that disease in a defined geographical region.[17] The first question is how do we know we have achieved this? This requires 2 components—the absence of new cases and the cure of all known cases. In Singapore, viral hepatitis is a notifiable disease,[18] hence all cases should be captured by the Ministry of Health. In reality, only acute cases are reported. Consequently, the capture of data on cases is incomplete and bulk data is not available to determine disease burden or outcome. Countries that have the most successful programmes (such as Australia) have a comprehensive notification system that detects new cases of chronic HCV, track outbreaks, monitor treatment, and outcomes. Australia estimates that 75% of the disease burden has been diagnosed, and are on the path to treatment and cure.[19] We can learn much from such infrastructure. Since viral hepatitis is already a notifiable disease in Singapore, setting up such a system could be possible. The benefits are potentially enormous, particularly in the detection of disease outbreaks, linkage to care and outcomes such as disease complications and mortality, and linkage to therapy. One big difference between Australia and Singapore is the much lower prevalence of HCV here—1.4%[20] compared to approximately 0.1%. A screening strategy for low prevalence countries needs to utilise a micro-elimination strategy[15] targeting pockets of high-risk patients which include blood transfusion recipients before 1990, renal dialysis patients, patients with liver disease, individuals with frequent transfusions or blood products, people who inject drugs and migrants from countries with high prevalence rates. HCV antibody testing should be routinely added to multiphasic health screening in addition of HBsAg. Overall, a targeted testing strategy for such high-risk groups will allow for a more precise picture of the burden of disease—a necessity in planning healthcare budgets and health resources. Ultimately, an affordable treatment strategy is needed for elimination, and such a strategy is being evaluated in Singapore. What HCV has today that enables the public health approach is a highly effective cure that can be universally delivered to large groups of infected patients. This, unfortunately, is what is missing in HBV today.

Returning to CHB, we have highly effective oral antiviral agents that are able to control disease.[21] A recent consensus workshop has proposed that loss of HBsAg can be called functional cure,[22] and should be the objective of therapy. This is a substantial milestone in the approach of CHB which has been thought to be lifelong and "incurable." However, there is increasing evidence of success in a functional cure, and Singapore has been one of the global centres taking a leading role in this field. The award of the Translational Clinical Research (TCR) Grant of $25 million for the eradication of HBV has consolidated a national effort for a HBV cure. The investigators of the grant comprise a national translational group of 29 researchers and scientists who have been working collaboratively on the eradication of CHB through a comprehensive approach via 3 integrated themes of examining host/viral interactions, target discovery with validation, novel agents, and experimental therapeutics. The team has found and characterised immune cells in CHB infection, as well as important proteins used by the virus to replicate. A novel animal model is now being validated and 8 compounds have been found to be active against HBV and are now being tested. In order to optimise a functional cure of CHB with existing therapy, we conducted a clinical trial to test the combination of interferon and nucleoside analogues, and preliminary data suggests that this can lead to a functional cure of CHB in about 11% of patients. However, before we can address the issue of elimination of HBV, we need better treatments similar to HCV that are able to cure high proportions of patients with short-term therapy. The infrastructure laid down in the push for HCV elimination can then be seamlessly utlised to treat HBV. In the interim, there are 10 new classes of compounds and 36 new agents[23] in clinical or preclinical testing that raise expectations that a functional cure is not too far away.

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Original Article

Outcomes of Patients Presenting with Primary or Secondary Atrial Fibrillation with Rapid Ventricular Rate to the Emergency Department

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Abstract

Introduction: Atrial fibrillation (AF) with rapid ventricular rate (RVR) is a common diagnosis in the Emergency Department (ED) requiring evaluation and treatment. We present the characteristics and outcomes of patients presenting with primary or secondary AF in a tertiary hospital ED. Materials and Methods: This retrospective cohort study included consecutive patients ≥21 years old, with a primary or secondary diagnosis of AF with RVR in the ED over a 1-year period from 1 January 2016 to 31 December 2016. Primary AF is defined as AF with no precipitating cause and secondary AF as AF secondary to a precipitating cause. Results: A total of 464 patients presented to the ED from 1 January to 31 December 2016 with primary and secondary diagnosis of AF with RVR; 44.8% had primary diagnosis of AF whereas 55.2 % had secondary AF. Overall admission rate from ED was high at 91.8% (primary 84.6% vs secondary 97.7%). Patients with primary AF were younger (68 vs 74 years, *P* <0.001), had lower rates of cardiovascular risk factors, and shorter length of stay (median 4 vs 5 days). Within 30 days of discharge, they had lower ED reattendance (16.3% vs 25.8%, *P* <0.001) and lower readmission (16.3% vs 25.8%, *P*<0.001). There was no mortality in the primary AF group (0% vs 9.8%, *P*<0.001). Conclusion: Currently, majority of patients with AF with RVR are admitted from the ED. Our study suggests patients with uncomplicated primary AF have lower adverse outcomes and some could potentially be treated as outpatients.

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Key words: Characteristics, Outpatients

Introduction

Atrial fibrillation (AF) is the most common arrhythmia managed by emergency medicine physicians.[1,2] The prevalence of AF in developed countries is estimated to be between 0.5 to 1.0%,[3] with AF accounting for 0.8% of Emergency Department (ED) visits in the United States from 1993 to 2004.[4] In Singapore, AF is the most common arrhythmia with an increasing trend. In a study done in 2008 among Chinese residents, the estimated prevalence of AF in Singapore was an estimated 2.6% in men and 0.6% in women, with an increase to 5.8% in adults more than 80 years and above.[5] However, this number has increased over recent years due to population ageing, increasing prevalence of comorbidities (diabetes, hypertension, ischaemic heart disease) and increased awareness and diagnosis of AF.[6] AF affects the quality of life. It increases the risk of stroke and heart failure; and overall mortality rate is approximately double compared to patients in normal sinus rhythm.[7,8] Patients with AF are also older and have a higher prevalence of comorbidities (diabetes, hypertension, cardiovascular disease).[9,10] All these make AF a major global health problem, imposing a heavy burden on healthcare systems

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worldwide, with increasing hospital admissions[11,12] and healthcare costs[13] over the recent years.

AF with rapid ventricular rate (RVR) (i.e. ventricular rate ≥100 beats/minute) is a common ED diagnosis that requires prompt evaluation and treatment. However, RVR can possibly be managed in the ED, avoiding hospital admissions and thus reducing overcrowding and healthcare costs. The challenge will be identifying low-risk patients suitable for outpatient management.

Patients coming to the ED can present with primary or secondary AF. Primary AF is defined as AF without a precipitating cause and secondary AF as AF precipitated by a secondary or reversible condition (e.g. surgery, sepsis, acute myocardial infarction, thyrotoxicosis or acute pulmonary disease).[14] Patients with a secondary diagnosis of AF may have different prognostic outcomes.[15]

This study outlines the characteristics of patients presenting with primary or secondary AF with RVR to a tertiary hospital ED and the burden of AF on the ED including the admission rate, length of stay, morbidity and mortality and ED reattendance.

Materials and Methods

Study Design

This study was a 1-year retrospective observational cohort study focusing on consecutive patients attending the ED with primary or secondary diagnosis of AF with RVR. The study was approved by the SingHealth Centralised Institutional Review Board.

Study Setting and Population

The study involved the ED of a single tertiary centre, Singapore General Hospital (SGH). It utilised Electronic Medical Record data of patients attending the ED with primary or secondary diagnosis of AF with RVR from 1 January to 31 December 2016. SGH is a tertiary centre in Singapore and the ED serves about 130,000 to 140,000 patients annually. The hospital has a national heart centre that provides both cardiology and cardiothoracic services.

Inclusion criteria included patients ≥21 years old, with a primary or secondary diagnosis of AF in the ED. We included only patients with AF with RVR, as this is the group of symptomatic patients who commonly require intervention and treatment in the ED. Patients' clinical data were extracted from the hospital's computerised medical records and all data were anonymised.

Data Collection

Data was collected from the Sunrise Clinical Manager (SCM) electronic database for patients attending the ED. The SCM database provides a unified patient record workflow and captures clinical information from the moment the patient enters the hospital to the moment of discharge, through to continued care in an outpatient setting. The International Classification of Disease (ICD) version 10 was used to classify and code all diagnoses and symptoms. Patients with first and second diagnosis listed as AF were extracted.

Study data were extracted and managed using the REDCap (Research Electronic Data Capture) tools hosted at SGH.[16] REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Patients' data were anonymised and reviewed by a first reviewer (2nd author) using an electronic spreadsheet including demographics, comorbidities, treatment in ED, diagnosis of primary or secondary AF, ED disposition, length of stay, 30-day morbidity and mortality and ED re-attendance and readmission. The data was subsequently reviewed and verified by a second reviewer (1st author). Any differences in conclusions were resolved with the last author. The CHA_2DS_2-VASc score was also calculated. We used the CHA_2DS_2-VASc score as this is the recommendation of the European Society of Cardiology (ESC)[17] and the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS)[18] to estimate stroke risk for AF patients. Consideration of oral anticoagulant (OAC) prophylaxis is recommended for patients with a score of 1. OAC use is a definite recommendation for patients with a score of 2 or greater and for those with a history of stroke or transient ischaemic attack.[18]

Statistical Analysis

All data analyses were performed using SPSS version 23 (SPSS, Chicago, IL). Categorical and continuous data were presented as frequencies with percentage and median with interquartile range (IQR), respectively. Association between categorical variables were assessed using chi-squared test. Statistical significance was generally set at a 2-tailed *P* value of less than 0.05.

Results

The study flowchart is shown in Figure 1. Between 1 January to 31 December 2016, there were 464 patients with primary or secondary diagnosis of AF with RVR in the ED. Two-hundred-and-eight patients (44.8%) had primary diagnosis of AF, whereas 259 patients (55.2%) had secondary AF with precipitating causes. Primary AF patients had a lower inpatient admission rate from ED; 84.6% of primary AF patients were admitted compared

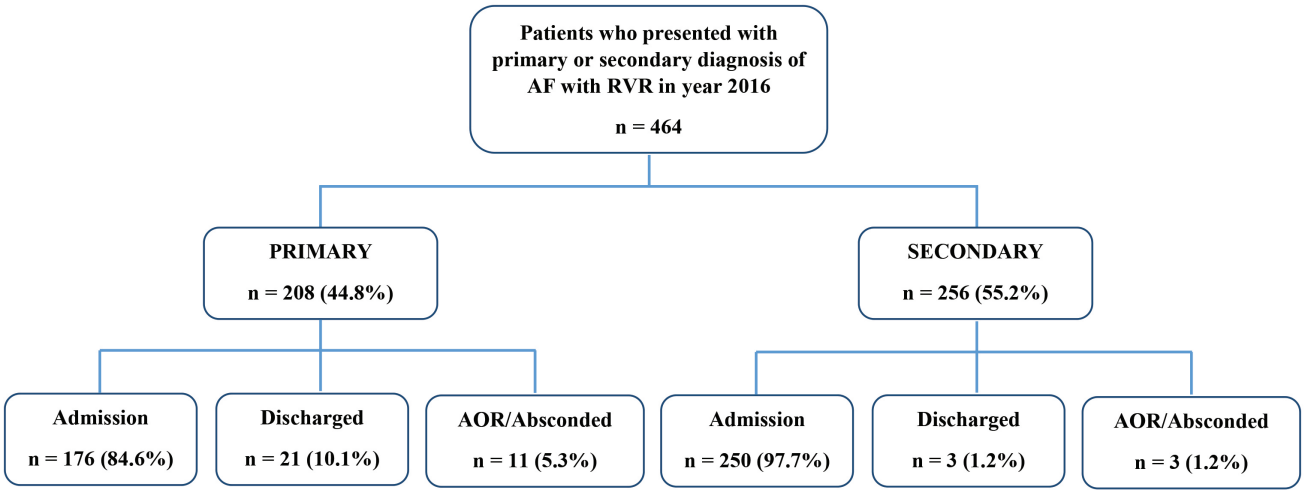

Fig. 1. Flowchart of patients presenting to the Emergency Department with atrial fibrillation and rapid ventricular rate. AF: Atrial fibrillation; AOR: Discharge at own risk; RVR: Rapid ventricular rate.

to 97.7% of secondary AF patients (P <0.001). A total of 10.1% of primary AF patients were discharged versus only 1.2% of secondary AF patients.

Table 1 shows the demographics, comorbidities, presenting symptoms, CHA_2DS_2-VASc score, treatment in ED and inpatient anticoagulation between primary and secondary AF patients. Median age of patients was 70 years old (IQR ranges, 62-81) and 45.3 % were men.

Secondary AF patients were older (median age of 74 years vs 67 years, P <0.001). A higher proportion of patients with secondary AF had cardiovascular risk factors compared to primary AF patients. Hypertension was the most prevalent cardiovascular risk factor (primary 65.9% vs secondary 71.9%). Secondary AF patients were more likely to have hypertension, diabetes, ischaemic heart disease, previous stroke and end-stage renal failure. They were also more likely to have a history of AF compared to primary AF patients.

Patients with primary AF with RVR were more likely to present with palpitations (45.7% vs 20.3%, P <0.001) and chest pain (22.1% vs 6.6%, P <0.001). A total of 55.8% of patients who presented to the ED with AF were not on prior antiplatelet or anticoagulation (primary 61.5% vs secondary 51.2%). Majority of patients (80.8%) had CHA_2DS_2-VASc score of ≥2 (primary 74.5% vs secondary 85.9%). More patients with primary AF had CHA_2DS_2-VASc score of 0 compared to secondary AF (11.5% vs 2.3%, P <0.001). Most of the patients were treated with rate control agents in the ED; 57.7% of patients with primary AF were treated with diltiazem compared to 35.2% of secondary AF patients (P <0.001). One patient with secondary AF underwent synchronised cardioversion in the ED due to haemodynamic instability. A total of 40.9% of primary AF patients were

Table 1. Characteristics of Patients Presenting to the Emergency Department with Atrial Fibrillation and Rapid Ventricular Rate

Characteristics	All n = 464 (%)	Primary AF n = 208 (%)	Secondary AF n = 256 (%)	*P* Value
Median age (IQR)	70 (62 – 81)	67 (60 – 76)	74 (63 – 83)	<0.001*
Male	210 (45.3)	99 (47.6)	111 (43.4)	0.399
Race				0.260
Chinese	364 (78.4)	160 (76.9)	204 (79.7)	
Malay	49 (10.6)	25 (12.0)	24 (9.4)	
Indian	26 (5.6)	8 (4.1)	18 (7.0)	
Eurasian	5 (1.1)	3 (1.4)	2 (0.8)	
Others	20 (4.3)	12 (5.8)	8 (3.1)	

AF: Atrial fibrillation; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; ESRF: End stage renal failure; IQR: Interquartile range; NIL: zero; NOACs: Novel oral anticoagulants

*Statistical significance (P <0.05).

Table 1. Characteristics of Patients Presenting to the Emergency Department with Atrial Fibrillation and Rapid Ventricular Rate (Cont'd)

Characteristics	All n = 464 (%)	Primary AF n = 208 (%)	Secondary AF n = 256 (%)	*P* Value
Medical history				
Hypertension	321 (69.2)	137 (65.9)	184 (71.9)	0.189
Diabetes mellitus	155 (33.4)	53 (25.5)	102 (39.8)	<0.001*
Hyperlipidaemia	264 (56.9)	113 (54.3)	151 (59.0)	0.346
Ischaemic heart disease	125 (26.9)	49 (23.6)	76 (29.7)	0.143
Acute myocardial infarction	50 (10.8)	18 (8.7)	32 (12.5)	0.228
Haemorrhagic/ischaemic stroke	66 (14.2)	20 (9.6)	46 (18.0)	0.011*
COPD	8 (1.7)	2 (1.0)	6 (2.3)	0.306
ESRF	33 (7.1)	9 (4.3)	24 (9.4)	0.045*
AF	231 (49.8)	89 (42.8)	142 (55.5)	0.007*
Prior anticoagulation or antiplatelet therapy				
NIL	259 (55.8)	128 (61.5)	131 (51.2)	0.031*
Warfarin	78 (16.8)	23 (11.1)	55 (21.5)	0.003*
NOACs	42 (9.1)	25 (12.0)	17 (6.6)	0.051
Aspirin	63 (13.6)	21 (10.1)	42 (16.4)	0.056
Clopidogrel	36 (7.8)	15 (7.2)	21 (8.2)	0.730
Presenting symptom				
Palpitations	147 (31.7)	95 (45.7)	53 (20.3)	<0.001*
Chest pain	63 (13.6)	46 (22.1)	17 (6.6)	<0.001*
Others	333 (71.8)	103 (49.5)	230 (89.8)	<0.001*
CHA_2DS_2-VASc score				
0	30 (6.5)	24 (11.5)	6 (2.3)	0.001*
1	59 (12.7)	29 (13.9)	30 (11.7)	0.001*
≥2	375 (80.8)	155 (74.5)	220 (85.9)	0.001*
Treatment instituted in ED				
Rate/rhythm control				
None	79 (17.0)	36 (17.3)	43 (16.8)	0.902
Diltiazem	210 (45.3)	120 (57.7)	90 (35.2)	<0.001*
Bisoprolol	61 (13.1)	37 (17.8)	24 (9.4)	0.009*
Digoxin	68 (14.7)	19 (9.1)	49 (19.1)	0.002*
Amiodarone	103 (22.2)	18 (8.7)	85 (33.2)	<0.001*
Verapamil	4 (0.9)	3 (1.4)	1 (0.4)	0.330
Others	7 (1.5)	2 (1.0)	5 (2.0)	0.467
Synchronised cardioversion				
Yes	1 (0.2)	0 (0.0)	1 (0.4)	1.000
No	0 (0.0)	208 (100.0)	255 (99.6)	1.000
Inpatient treatment				
Anticoagulation				
None	51 (11.0)	21 (10.1)	30 (11.7)	0.655
Aspirin	146 (31.5)	58 (27.9)	88 (34.4)	0.159
Clopidogrel	97 (20.9)	44 (21.2)	53 (20.7)	0.909
Warfarin	104 (22.4)	31 (14.9)	73 (28.5)	<0.001*
Novel oral anticoagulant	145 (31.3)	85 (40.9)	60 (23.4)	<0.001*

AF: Atrial fibrillation; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; ESRF: End stage renal failure; IQR: Interquartile range; NIL: zero; NOACs: Novel oral anticoagulants

*Statistical significance (P <0.05).

started on novel oral anticoagulant (NOAC) as inpatients, compared to 23.4% of secondary AF patients.

Table 2 shows the outcomes of patients with primary and secondary AF. A total of 426 patients (91.8%) were admitted. Secondary AF patients had higher hospital admission rates (97.7% vs 84.6%, P <0.001) and longer length of stay (median, 5 days vs 4 days). They had higher ED reattendance (23.8% vs 13.5%, P <0.001) and readmission rate (25.8% vs 16.3%, P <0.001) within 30 days of discharge compared to the primary AF group. Thirty-day mortality for secondary AF patients was also higher (9.8% vs 0%). Four patients each in the primary and secondary AF group had ischaemic stroke whereas 1 patient in the primary AF group had intracranial haemorrhage.

Discussion

In this study of 464 patients attending the ED of a single tertiary centre in Singapore with primary and secondary diagnosis of AF with RVR, the demographics were similar to other global cohorts for baseline characteristics and comorbidities.[19-22] Overall admission rate from ED was high (91.8%). There was a high proportion of patients with primary AF (84.6%) who were admitted. This was different from other studies where a lower percentage of patients with primary AF without an acute medical cause were admitted.[23,24] A population-based study done in Alberta[23] on ED presentations for AF and flutter showed ED admission of 26.9%, whereas a study done in 2 urban Canadian EDs on patients with AF with no acute underlying medical cause[24] had admission rate of 15.3% from ED.

There were various factors for the high admission rate of patients with primary AF in our study's ED. Whereas centres in other countries do electrical cardioversion for acute onset of AF (<48 hours)[25-27] in the ED, this is not usually carried out in our local EDs. In the ED of our study, we do not have access to trans-esophageal echocardiogram (TEE) prior to cardioversion. It is also difficult and time consuming to counsel patients with regard to cardioversion and subsequent anticoagulation, which makes it even more challenging in a busy ED environment. All these are the possible barriers to why patients are admitted.

There were more patients who presented with secondary AF with RVR. The secondary causes of AF included sepsis, congestive cardiac failure, thyrotoxicosis and other intercurrent illness (e.g. pulmonary disease, chronic obstructive pulmonary disease [COPD]). The most common precipitating cause for secondary AF is congestive cardiac failure (51.4%) followed by sepsis (34.7%) in this study. Patients with secondary AF had a longer length of stay, higher ED reattendance, readmission rate and 30-day mortality rate. This could be due to various factors. Firstly, patients in the secondary AF group were older and a higher proportion had cardiovascular risk factors. Secondly, the primary disease precipitating the AF could attribute to the higher mortality rate as compared to patients in the primary AF group with no precipitating cause. There have been studies[15,28,29] which suggested that concomitant AF with congestive cardiac failure and sepsis may have a worse effect on prognosis. A recent study by Clare L Atzema et al showed that such group of patients with secondary AF have high short- and long-term mortality rates and mortality was higher than in patients with primary diagnosis of AF.[15]

In this study, patients with primary AF with RVR were

Table 2. Outcomes in Patients with Primary Atrial Fibrillation vs Secondary Atrial Fibrillation

Outcomes	All n = 464 (%)	Primary AF n = 208 (%)	Secondary AF n = 256 (%)	*P* Value
Disposition				
Hospital admission	426 (91.8)	176 (84.6)	250 (97.7)	<0.001*
Discharge from ED	24 (5.2)	21 (10.1)	3 (1.2)	<0.001*
AOR/absconded	14 (3.0)	11 (5.3)	3 (1.2)	<0.001*
Length of stay (days)				
Median (IQR)	4 (3 – 7)	4 (3 – 5)	5 (3 – 8)	<0.001*
30-day morbidity				
Ischaemic stroke	8 (1.7)	4 (1.9)	4 (1.6)	1.000
Intracranial and extracranial haemorrhage	1 (0.2)	1 (0.5)	0 (0.0)	0.449
30-day mortality	25 (5.4)	0 (0.0)	25 (9.8)	<0.001*
Reattendance to ED within 30 days discharge from ED/ward	89 (19.2)	28 (13.5)	61 (23.8)	<0.001*
Readmission to inpatient within 30 days of discharge	100 (21.6)	34 (16.3)	66 (25.8)	<0.001*

AF: Atrial fibrillation; AOR: Discharge at own risk; ED: Emergency department; IQR: Interquartile range
*Statistical significance (P <0.05).

younger with lower rates of cardiovascular risk factors. A higher proportion of them had CHA_2DS_2-VASc score of 0 compared to the secondary AF group. They had shorter length of stay, lower ED reattendance and readmission. Risk of stroke for this group of patients was low and similar to the secondary AF group. There was no mortality in the primary AF group. In comparison to the secondary AF group, primary AF patients have lower adverse outcomes and can be an opportunity for outpatient management and discharge from ED. In our study, 40.9% of primary AF patients were started on NOAC as inpatients, compared to 14.9% on warfarin. It may be worth considering discharging AF patients with a NOAC from ED instead of admitting them as inpatients for anticoagulation which is the usual practice. This may help to reduce hospital overcrowding and healthcare costs.

With an increasing prevalence of AF in Singapore, there can be an opportunity for outpatient management in the ED. In Singapore, most EDs have an emergency observation ward or short stay unit. These observation wards are for stable patients with conditions that can likely be discharged after 8 to 24 hours. Patients can be monitored on telemetry while in the observation ward. In Singapore, there is at least 1 ED with an AF protocol in their observation unit. In the study's ED, there is no emergency observation ward protocol for patients with AF with RVR. With the data collected, future plans include implementation of an AF pathway and observation protocol, looking into more efficient processes to reduce length of stay and potentially discharging patients within 24 hours. There had been studies done on ED observation unit for AF. Most of them focused on acute onset of AF <48 hours with discharge from ED postcardioversion.[25,27] There were more recent studies on the impact of ED observation unit management algorithm and pathway for AF.[26,30] These pathways included selecting patients with primary AF in the ED who then underwent rate control, cardioversion for those with acute AF and initiation of anticoagulation based on CHA_2DS_2-VASc score.[31] They showed that implementation of an ED observation unit AF algorithm was associated with significantly decreased hospital admissions without increasing the rates of return ED visits, hospitalisation, or adverse events within 30 days.[26]

Limitations

This study was a retrospective study done in a single tertiary centre in Singapore. Therefore, the results may have limited applicability and generalisability to other centres. Patients with main (first) and second diagnosis of AF were extracted from our centre's computerised medical records. It could be possible that patients with AF listed other than the first and second diagnoses were also eligible but missed in the selection process. We included only patients with AF with RVR as this was the group of patients most commonly encountered in our ED who required intervention and treatment. Therefore, there could be a large group of patients with AF who were excluded as they did not have RVR. All data were de-identified and processed by a first investigator and reviewed/checked by a second investigator. However, we did not check inter-rater reliability in this study, which is a major limitation. The data could be subjected to bias and subjectivity. There could be errors in data processing and missing out essential information in the process.

Conclusion

Currently, the majority of patients with primary or secondary AF with RVR are admitted from the ED. Our study suggests that patients with primary AF have lower adverse outcomes and can potentially be treated as outpatients. It may be worth looking into improving processes for an AF pathway within the ED for such patients.

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Original Article

Survey of Respiratory Virus in Patients Hospitalised for Acute Exacerbations of Heart Failure – A Prospective Observational Study

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Abstract

Introduction: Respiratory virus (RV) infections have been implicated in acute exacerbation of cardiopulmonary conditions. This study aimed to determine the prevalence of RV infections in patients admitted to the cardiology unit with acute decompensated heart failure (ADHF) in a tertiary hospital in Singapore. Materials and Methods: This was a single-centre, prospective observational study. A total of 194 adults (aged >21) admitted to the Singapore General Hospital with ADHF were recruited. A nasopharyngeal swab was taken for multiplex polymerase chain reaction (PCR) detection of influenza virus, rhinovirus, parainfluenza virus (HPIV), human coronavirus (HcoV), adenovirus, human bocavirus (HboV), human metapneumovirus (hMPV), and respiratory syncytial virus (RSV). Results: Twenty-five (13%) had RVs detected by RV multiplex PCR. These comprised 9 rhinoviruses (36%), 4 influenza A viruses (16%), 3 HPIV (12%), 3 HCoV (12%), 2 adenoviruses (8%), 1 human HBoV (4%), 1 hMPV (4%), and 1 RSV (4%). Symptoms-wise, cough was significantly more common in the PCR-positive group (48% vs 24%, *P* = 0.02). There were no statistically significant differences in laboratory investigations (haemoglobin, leukocytes, platelets, creatine kinase, creatine kinase-muscle/brain, troponin T), and radiology findings between RV PCR-positive and -negative groups. The PCR-positive group did not have increased mortality or length of hospital stay. Conclusion: This study identified a considerable burden of RVs in our ADHF cohort, and highlights the need for prevention of RVs in this group of patients. We also recognised the difficulty with clinical diagnosis of RVs in ADHF patients.

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Key words: Cardiac failure, Heart disease, Influenza, Respiratory tract infections, Respiratory virus infections

Introduction

Congestive heart failure (CHF) is a growing global health problem, affecting 11.8% of people over the age of 60.[1] Acute decompensated heart failure (ADHF) is the leading reason for hospitalisation in CHF patients, and is associated with substantial rates of mortality and morbidity of 5% to 14%.[2,3] In Singapore, heart failure (HF) is also associated with considerable cardiac and non-cardiac mortality.[4] Respiratory virus (RV) infections have been implicated in acute exacerbation of cardiopulmonary conditions.[5] In particular, influenza and respiratory syncytial viruses (RSV) were diagnosed in 21% of elderly patients with underlying cardiac and/or pulmonary comorbidities hospitalised for acute cardiopulmonary exacerbations.[6] Likewise, another study also showed that influenza, RSV, rhinovirus, coronavirus, and human metapneumovirus (hMPV) were detectable in 17% of elderly patients admitted to critical care units with acute cardiorespiratory failures.[5] In addition, epidemiological studies and randomised controlled trials have demonstrated the benefit of influenza vaccination in reducing the risk of cardiovascular and cerebrovascular events.[7-18]

However, most of the patients in these studies had an underlying respiratory, rather than cardiac condition, precluding any proper characterisation of respiratory infections in a cohort of ADHF patients. In fact, the prevalence of viral respiratory pathogens in patients admitted with ADHF has not been reported to date. This study aimed to establish the prevalence of RV infections in adults with underlying cardiac disorders admitted with ADHF.

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Materials and Methods

Subjects

Subjects were recruited from the cardiology wards of the Singapore General Hospital. All adults (aged >21) admitted through the accident and emergency department with a diagnosis of New York State Heart Association (NYHA) Class III or IV acute heart failure were eligible. Patients diagnosed with ADHF were flagged for recruitment. Any patient with end stage renal failure (ESRF) (defined as chronic kidney disease [CKD] stage >4 with fluid overload) or exacerbation of chronic obstructive pulmonary disease (COPD) was excluded. All subjects gave informed consent. Our research was carried out in compliance with the Helsinki Declaration and approval was obtained from our hospital's Institutional Review Board (SingHealth Centralised Institutional Review Board, Reference No.: 2012/650/F).

Enrolment and Study Period

Recruitment took place from 1 December 2012 to 31 May 2013, which contained the 2 flu seasons in the tropics following the Northern and Southern Hemisphere winters.[19] Demographic, medical and drug history, presenting clinical symptoms and physical findings were recorded. Chest radiographs and blood samples for full blood count, electrolytes, and cardiac enzymes (troponin T, creatinine kinase [CK], and creatinine kinase-muscle/brain [CK-MB]) were obtained on all patients. Patients were followed up for 28 days from recruitment.

Respiratory Virus Polymerase Chain Reaction (PCR)

Subjects underwent nasopharyngeal swabs using Dacron-tipped swabs within 48 hours of admission, which were analysed within 24 hours by RV multiplex PCR (Seegene Anyplex II 16 Detection Multiplex PCR kit, Seegene) according to the manufacturer's instructions using the Bio-Rad CFX96 Real-Time PCR Detection System (CA, USA). In brief, the swabs were added to 1.0 ml of 1x phosphate buffered saline and vortexed vigorously. The swab suspension (500 µL) was then added to the NucliSens easyMAG automated instrument (BioMerieux, France) for total nucleic acid extraction. The final volume of elution was 55 µL. Of this, 8 µL of nucleic acid extract was used for PCR performed using the Seegene Anyplex II RV16 Detection Multiplex PCR kit (Seegene, Korea). This assay simultaneously detected 16 types of human respiratory viral pathogens (influenza A and B, human parainfluenza virus (HPIV) 1/2/3/4, RSV subtypes A and B, hMPV, human coronavirus (HCoV) (229E/NL63/OC43), rhinovirus A/B/C, enterovirus, adenovirus and human bocavirus (HboV) 1/2/3/4. The PCR reaction was performed on the Applied Biosystems 9700 thermocycler and the results were read by capillary electrophoresis (QIAxcel, Qiagen, Germany).

Outcome Measurements

Primary outcome was detection of RV by PCR in a nasopharyngeal swab. Secondary outcomes (assessed in all patients) included clinical, laboratory, and radiological features, 28-day mortality, and length of hospital stay (LOS).

Statistics

Data was analysed using SPSS software (version 13 for Windows; SPSS Inc, US). Descriptive statistics of data were expressed as frequencies, percentages, mean ± standard deviation (SD). Differences in characteristics between participants were performed with the χ^2/Fisher's exact test; 95% confidence intervals were reported, and 2-sided *P* value of less than 0.05 was taken to be statistically significant.

Results

Subjects

Between 1 December 2012 and 31 May 2013, 508 patients admitted with the primary diagnosis of ADHF were screened for eligibility. A total of 267 patients were excluded, and of 241 eligible patients, 194 patients (males, 71%) gave informed consent. All patients completed 28 days' follow-up after recruitment (Fig. 1).

Baseline demographics were similar in patients with or without positive RV PCR and are summarised in Table 1. The mean age of the study population was 64.2 (standard

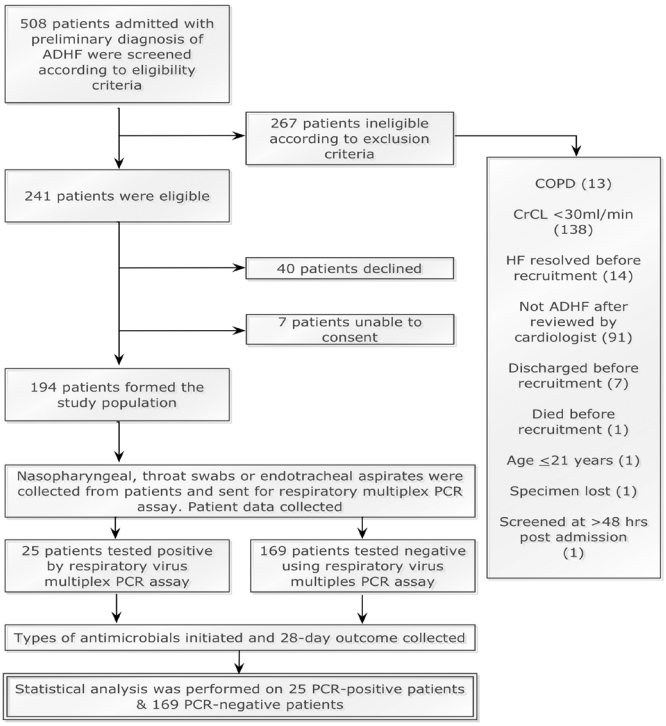

Fig. 1. Flow chart illustrating the recruitment of patients for the present study. ADHF: Acute decompensated heart failure; COPD: Chronic obstructive pulmonary disease; CrCl: Creatinine clearance; HF: Heart failure; PCR: Polymerase chain reaction.

Table 1. Demographic and Clinical Data of Studied Patients

Demographics	All (n = 194)	PCR+ (n = 25)	PCR- (n = 169)	*P* Value
Age, mean (SD)	64.2 (11.9)	62.0 (10.1)	64.5 (12.2)	0.28
Gender, male (%)	138 (71)	19 (76)	119 (70)	0.64
Race (%)				
Chinese	134 (69)	14 (56)	120 (71)	0.13
Malay	35 (18)	10 (40)	25 (15)	0.0022
Indian	24 (12)	1 (4)	23 (14)	0.17
Others	1 (1)	0 (0)	1 (1)	1.00
Active smoker (%)	28 (14)	2 (8)	26 (15)	0.59
Obesity (%)	18 (9)	3 (12)	15 (8.9)	0.71
Previous heart failure (%)	104 (54)	13 (52)	91 (55)	0.83
Hypertension (%)	139 (72)	18 (72)	121 (71)	1.00
Diabetes mellitus (%)	97 (50)	11 (44)	86 (51)	0.67
Hyperlipidaemia (%)	134 (69)	19 (76)	115 (68)	0.49
Ischaemic heart disease (%)	112 (58)	13 (52)	99 (59)	0.67
Cardiac arrhythmia (%)	46 (24)	6 (24)	40 (24)	1.00
Valvular heart disease (%)				
Valve stenosis	13 (7)	2 (8)	11 (7)	0.68
Regurgitation	34 (18)	3 (12)	31 (18)	0.58
Valve replacement surgery	10 (5)	1 (4)	9 (5)	1.00
Renal impairment (%)	26 (13)	3 (12)	23 (14)	1.00
Anaemia (%)	37 (19)	4 (16)	33 (20)	0.79
Rheumatic heart disease (%)	9 (5)	1 (4)	8 (5)	1.00
Mortality (%)	1 (1)	0 (0)	1 (1)	1.00
Length of stay, mean (SD)	6.80 (6.5)	6.92 (3.9)	6.80 (6.5)	0.90

PCR: Polymerase chain reaction; SD: Standard deviation

deviation [SD] 11.9) years, which is consistent with the demographics of HF patients in Singapore.[20] Our patients were predominately Chinese (69%), consistent with the demographics of the local population. The prevalence of pre-existing conditions in the study population included HF (54%), ischaemic heart disease (58%), hypertension (72%), diabetes mellitus (50%), hyperlipidaemia (69%) and cardiac arrhythmias (24%). Of note, there were more Malays in the RV PCR-positive group (40%) compared with the PCR-negative group (18%).

Length of Hospital Stay and Mortality

The overall mean LOS was 6.80 days (SD 6.5) (Table 1). No significant difference in the LOS was found between PCR-negative and PCR-positive patients (mean 6.80 vs 6.92 days, respectively). No mortality was observed during 28-day follow-up in the PCR-positive group. One patient in the PCR-negative group died due to end-stage HF from underlying dilated cardiomyopathy; he underwent extracorporeal membrane oxygenation (ECMO) and ventricular assist device (VAD) placement but succumbed to complications related to bowel ischaemia.

PCR Findings and Clinical Characteristics

RV PCR results are summarised and shown in Figure 2 and Table 2. PCR was positive in 25 patients (13%), with the commonest viruses being rhinoviruses (36%), influenza A (16%), HPIV (12%) and HCoV (12%). One patient had 2

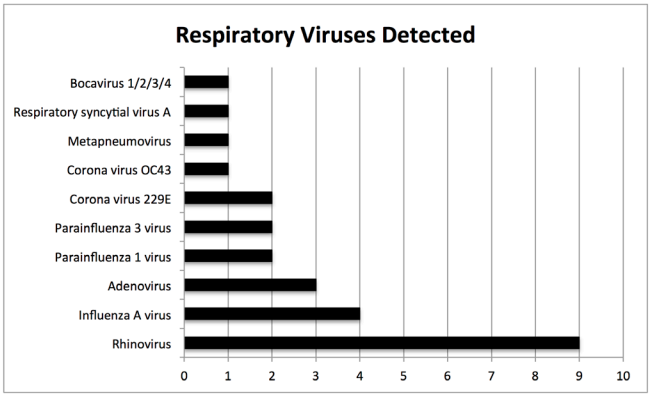

Fig. 2. Graph showing the frequency of respiratory viruses identified by PCR in hospitalised patients with ADHF. One patient tested positive for both adenovirus and parainfluenza 1 virus in single swab. ADHF: Acute decompensated heart failure; PCR: Polymerase chain reaction.

Table 2. ADHF Patients with Positive Respiratory Virus PCR

Number of Subjects with Positive PCR (n = 25)	No. of Isolates (%)
Rhinovirus*	9 (36)
Influenza A virus†	4 (16)
Adenovirus	2 (8)
Coronavirus 229E*	2 (8)
Coronavirus OC43	1 (4)
HPIV1	1 (4)
HPIV1 + adenovirus	1 (4)
HPIV3	2 (8)
hMPV	1 (4)
Bocavirus	1 (4)
RSV A	1 (4)

hMPV: Human metapneumovirus; HPIV: Human parainfluenza virus; PCR: Polymerase chain reaction; RSV: Respiratory syncytial virus
*One patient was recruited twice, and had 2 viruses: rhinovirus in the first admission and coronavirus 229E in the second admission 28 days later.
†Two patients received oseltamivir therapy against influenza A after testing positive by PCR.

Table 3. Clinical Symptoms and Signs of ADHF Patients

Symptoms	PCR+ (n = 25) (%)	PCR- (n = 169) (%)	*P* Value
Cough	12 (48)	40 (24)	0.02
Sputum	5 (20)	18 (11)	0.19
Fever or sweating	2 (8)	19 (11)	1.00
Chills	1 (4)	1 (1)	0.24
Chest pain or tightness	11 (44)	52 (31)	0.25
Runny nose	0 (0)	1 (1)	1.00
Headache	1 (4)	1 (1)	0.24
Fatigue	0 (0)	3 (2)	1.00
Dypsnoea	22 (88)	160 (95)	0.19
Palpitations	1 (4)	18 (11)	0.48
Loss of appetite	1 (4)	8 (5)	1.00
Limb swelling	11 (44)	90 (53)	0.40
Abdominal pain	1 (4)	2 (1)	0.34
Abdominal distension	2 (8)	19 (11)	1.00
Giddiness	2 (8)	5 (3)	0.22
Abnormal chest sounds	24 (96)	154 (91)	0.70
Cardiac arrhythmia	0 (0)	12 (7)	0.37
Elevated JVP	12 (48)	80 (47)	1.00

GCS: Glasgow Coma Scale; JVP: Jugular venous pressure; PCR: Polymerase chain reaction

viruses (adenovirus and HPIV1) on the same swab. Another patient was readmitted and enrolled a second time 28 days later, and tested positive for rhinovirus and HCoV 229E on the 2 different occasions. Most PCR-positive patients were not prescribed antivirals, except for 2 influenza A-positive patients who received oseltamivir within 24 hours of admission upon receipt of PCR results.

Clinical findings of all patients upon admission are summarised in Table 3. Cough was more common among PCR-positive patients (48% vs 24%, $P = 0.02$). Other symptoms including sputum, dyspnoea and limb swelling were similar between PCR-positive and PCR-negative groups. Subjective symptoms of fever or sweating were reported in 19 patients with negative PCR, versus 2 patients with positive PCR ($P = 1.00$), but only 1 had documented fever (38.5°C). This patient was diagnosed with bacterial community-acquired pneumonia in addition to ADHF and tested negative for RVs.

Laboratory and Radiological Investigations

Laboratory results are summarised in Table 4. In summary, there were no statistically significant differences in laboratory findings between PCR-positive and -negative patients. Chest radiology findings also showed no significant differences between both groups (Table 5).

Discussion

Historically, multiple epidemiological studies have observed an increase in hospitalisation and mortality due to cardiopulmonary diseases during the winter seasons when RVs are circulating.[21] However, most of these studies recruited patients with both chronic pulmonary and cardiac conditions.[5,6,21,22] Although health policymakers are aware that influenza may cause serious illness in patients with COPD or ischaemic heart disease,[6,23] the impact of RVs in ADHF patients is yet to be defined. Therefore, we surveyed the prevalence of RVs in patients hospitalised for ADHF, as a first step in identifying a possible link between RV and HF. Our study shows that RVs are present in 13% of patients admitted with primary diagnosis of ADHF during the flu seasons. Our results thus highlight a considerable burden of RVs in ADHF patients.

In our study, rhinovirus was the most common pathogen detected. Rhinovirus has been implicated in exacerbations of chronic cardiopulmonary diseases in the elderly,[22] and even positively associated with pneumonia, exacerbations of COPD and CHF in older adults.[24] Since human rhinovirus is the most frequent cause of acute respiratory tract illnesses worldwide, its role as a precipitant of cardiac decompensation warrants further study.[25] Other less common viruses identified in this study were adenovirus (8%), hMPV (4%), HBoV (4%), RSV (4%), HPIV (12%), and coronavirus (12%). Adenovirus is a cardiotropic virus that has been implicated in myocarditis;[26] hMPV infection has

Table 4. Initial Laboratory Findings of Patients Admitted with Acute Decompensated Heart Failure

Laboratory Findings Mean (SD)	PCR+ (n = 25)	PCR- (n = 169)	*P* Value	95% Confidence Interval	
				Lower	Upper
WBC (x10^9/L)	9.14 (2.62)	8.32 (3.22)	0.12	-1.88	0.24
ALC (x10^9/L)	1.90 (0.80)	1.81 (0.90)	0.62	-0.44	0.27
ANC (x10^9/L)	6.22 (2.03)	5.63 (2.73)	0.21	-1.51	0.34
CRP (mg/L)	23.44 (45.93)	36.74 (59.33)	0.43	-21.46	48.07
Procalcitonin (ug/L)	6.79 (17.32)	0.45 (0.84)	0.31	-19.66	6.98
Haemoglobin (d/dL)	12.94 (2.627)	12.82 (3.10)	0.85	-1.28	1.06
Platelet (x10^9/L)	251.72 (61.48)	226.74 (76.77)	0.08	-563.64	2.68
ALP (u/L)	85.48 (47.82)	90.21 (47.18)	0.68	-18.19	27.66
ALT (u/L)	38.00 (42.13)	36.17 (34.20)	0.85	-21.68	18.03
AST (u/L)	52.45 (41.37)	47.81 (62.04)	0.67	-26.27	16.98
Bilirubin (umol/L)	19.90 (9.96)	25.15 (20.51)	0.06	-0.33	10.81
NTProBNP (pg/mL)	7465.16 (6141.13)	5672.97 (6942.68)	0.25	-4945.77	1361.39
Creatinine (umol/L)	109.70 (44.94)	106.42 (36.18)	0.74	-23.39	16.83
CCT (umol/L)	77.24 (41.32)	62.58 (26.28)	0.10	-32.12	2.79
Creatine kinase (u/L)	386.43 (760.93)	162.43 (143.13)	0.17	-553.70	-105.69
CK-MB (ug/L)	8.75 (18.78)	4.31 (4.95)	0.27	-2.59	3.71
Troponin T (ug/L)	0.37 (0.90)	0.11 (0.35)	0.18	-0.65	0.13

ALC: Absolute lymphocyte count; ALP: Alkaline phosphatase; ALT: Alanine transaminase; ANC: Absolute neutrophil count; AST: Aspartate transaminase; CCT: Creatinine clearance test; CK-MB: Creatine kinase-muscle/brain; CRP: C-reactive protein; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PCR: Polymerase chain reaction; WBC: White blood cell count

Table 5. Chest X-Ray Findings of Patients on Admission with Acute Decompensated Heart Failure

X-Ray Findings	PCR+ (n = 25)	PCR- (n = 169)	*P* Value
Pulmonary oedema (%)	3 (12)	16 (10)	0.72
Cardiomegaly (%)	20 (80)	127 (75)	0.80
Bilateral pleural effusions (%)	9 (36)	57 (34)	0.83
Consolidation (%)	2 (8)	18 (11)	1.00

PCR: Polymerase chain reaction

also been associated with acute exacerbations in patients with underlying cardiopulmonary disease.[27]

In this study, more Malays were PCR-positive compared with other local races (Table 1). Similarly, a previous study by Pang et al also noted Malay ethnicity to be positively associated with influenza-A (H1N1) and coxsackie/echovirus mono-infections.[28] It was hypothesised that genetic differences may result in weaker immune responses against specific RVs in Malays compared to other local ethnicities; more studies are needed to understand this relationship.

In our study, only cough was significantly more common in PCR-positive ADHF patients ($P = 0.02$). Given the many overlapping clinical features (including cough, sputum and dyspnoea) between RV and ADHF, the diagnosis of concurrent RV infections in ADHF patients could be challenging and often overlooked. This can be especially true in the elderly, in whom classical RV symptoms such as fever, sore throat or myalgia are often absent.[29] Furthermore, laboratory parameters such as leukocyte counts and C-reactive protein (CRP) lack sensitivity and specificity for the diagnosis of RV infections,[30] and indeed were not different in this cohort, whether PCR-positive or negative (Table 4). Hence neither symptomatology nor blood tests can reliably indicate which ADHF patient might be concomitantly having, or might have had a recent RV infection. Findings from our study do not support routine screening of all ADHF patients for RV, as there were no differences in the overall management, mortality or LOS in patients with or without RV positivity.

To date, the causal relationship between RV infection and cardiac disease are mostly supported indirectly by influenza vaccine studies, which showed that vaccinations reduced the risk of acute coronary syndromes and strokes in high-risk patients.[7,9-18] Further studies to identify the mechanistic link between RV infections and acute cardiac events could lead to the development of novel preventative and therapeutic interventions.

Conclusion

Our study identified a considerable burden of RVs in ADHF. However, there is a general lack of awareness of comorbid RVs, given the difficulty with clinical diagnosis. Given the high morbidity and mortality of HF during acute exacerbations, prevention of precipitants is an important

component of care. Looking forward, future studies should further explore the role of preventive measures such as vaccinations in ADHF.

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Original Article

Comparison between Single and Double Cleavage-Stage Embryo Transfers, Single and Double Blastocyst Transfers in a South East Asian In Vitro Fertilisation Centre

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Abstract

Introduction: This study investigated the differences in clinical pregnancy rate (CPR), live birth rate (LBR) and multiple pregnancy rate (MPR) between double cleavage-stage embryo transfers compared to single and double blastocysts stage embryo transfers in a single academic medical centre. Materials and Methods: This was a retrospective cohort study performed at the KK Women's and Children's Hospital In Vitro Fertilisation (KKIVF) Centre of all women who underwent fresh-cycle in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) cycles over a 5-year period. The outcome measures were CPR, LBR and MPR. The study included 5294 cycles, of which 539 patients underwent single embryo transfer (SET); 4533 patients underwent double embryo transfer (DET); 84 patients underwent double blastocyst transfer (DBT); and 65 patients underwent single blastocyst transfer (SBT). Results: The mean age of patients undergoing single blastocysts stage embryo transfer was lower than the other 2 groups. The DET, single and double blastocysts stage embryo transfer groups achieved similar LBR (33.9%, 38.7%, 35.4%, *P* >0.05) and CPR (42.4%, 46.2%, 46.9%). Conclusion: We found that single blastocysts stage embryo transfer is associated with similar LBR and CPR compared to double blastocysts stage embryo transfer and DET, with lower MPRs, and should be offered as standard practice, where possible.

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Key words: Infertility, Pregnancy outcomes

Introduction

The development of a reliable blastocyst culture system presents the opportunity to perform single blastocyst stage embryo transfer that avoids multi-pregnancies and its attendant morbidities, while maintaining pregnancy rates of cleavage-stage double embryo transfers (DETs). Blastocyst culture has proven to have more favourable outcomes by identifying embryos that are most able to establish a pregnancy.[1,2] A prospective randomised trial reported a higher pregnancy rate among women undergoing a single blastocyst transfer (SBT) versus a cleavage-stable embryo transfer.[3,4] Studies have also shown that SBTs have significantly less multiple pregnancy rates while maintaining clinical pregnancy rates (CPRs).[5,6] The strategy of performing single embryo transfer (SET) has been implemented in our institution over the past few years. Here, we asked if there were differences between double cleavage-stage embryo transfers compared to single and double blastocysts stage embryo transfers in a retrospective cohort study performed in KK Women's and Children's Hospital (KKH).

Materials and Methods

In this retrospective cohort, we included a total of 5414 consecutive fresh-cycle assisted reproductive technique (ART) performed at the KKH In Vitro Fertilisation (KKIVF)

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Centre. We included all cases that underwent fresh-cycle ART for single cleavage-stage embryo transfers on Day 2 to 3, double cleavage-stage embryo transfers on Day 2 to 3, double blastocyst transfers (DBTs) and SBTs over a 5-year period between 2009 to 2014. We then followed them up for a 1-year period thereafter to obtain the total number of live births.

We excluded 132 cycles, where there were more than 2 cleavage embryos (n = 130) or more than 2 blastocysts transferred (n = 2).

The outcome measures we looked at were CPR, live birth rate (LBR) and multiple pregnancy rate (MPR). CPR is defined as the presence of gestational sac on transvaginal scan at 6 weeks gestation. LBR is defined as the number of deliveries that resulted in at least 1 live born neonate (>24 weeks gestation). Patients were encouraged to inform KKH if deliveries were conducted in other hospitals. However, of note, some patients were lost to follow-up after the IVF cycles and may not have reported after delivery. MPR refers to the number of deliveries that resulted in 2 or more live born neonates (>24 weeks gestation). Miscarriage was defined as a clinical pregnancy that ended up in pregnancy loss prior to 24 completed weeks' gestation.

Data were extracted for statistical analysis using SAS software version 9.3 for Windows (SAS, Inc. Cary, NC). Baseline demographics and clinical features were compared among SET, DET, SBT and DBT using analysis of variance (ANOVA) for continuous variables and Fisher's exact test for categorical variables. To investigate the association between number of oocytes obtained with CPR and LBR, we used multivariable logistic regression analysis and adjusted the odds ratios for age. Statistical significance was set at $P \leq 0.05$.

Results and Discussion

Of the patients who underwent ART (n = 5294), a total of 539 patients underwent SET, 4533 patients underwent DET, 84 patients underwent DBT and 65 patients underwent SBT. Demographic details are illustrated in Table 1. Patients who underwent SET were significantly older compared to patients undergoing DET, single blastocysts stage embryo transfer and double blastocysts stage embryo transfer (mean age 36.5 vs 34.4, 33.5, 35.8, P <0.001). SET patients had a lower number of oocytes retrieved (5.6 vs 14.2, 17.8, 20.1, P <0.001), and lower CPR (16.0% vs 42.5%, 45.2%, 42.9%, P <0.001) and LBR (11.7% vs 34.0%, 38.1%, 36.9%, P <0.001) than the other 3 groups. Patients undergoing SET in our institution had only 1 usable embryo for transfer, and are therefore of poor prognosis. Thus, the SET group was not used for comparison with the other groups.

Table 1. Demographics

	Double Day 2 to 3 Embryo Transfer	Single Blastocyst Transfer	Double Blastocyst Transfer	*P* Value
Total no. of transfers	4533	84	65	
Age	34.4 ± 3.7	33.5 ± 3.5	35.8 ± 4.2	<0.001
No. of oocytes obtained	14.2 ± 8.1	17.8 ± 8.5	20.1 ± 11.6	<0.001

Patients who underwent single blastocysts stage embryo transfer were significantly younger than those who had DET and DBT (33.5 vs 34.4, 35.8, P <0.001). Single blastocysts stage embryo transfer patients also had similar CPR and LBR as compared to DET and DBT patients (Table 2). There was no multiple pregnancy live birth deliveries in single blastocysts stage embryo transfer patients in contrast to patients who had DET and DBT.

Next, we analysed the neonatal outcomes of the patients who delivered in our centre (Table 3). Among the singleton pregnancies, there was a similar rate of term deliveries, mean gestational age (GA) and birth weight (BW). However, among the multiple pregnancies, there was a significantly higher rate of full-term deliveries in the double blastocysts stage embryo transfer group compared to the DET group (83.3% vs 38.2%, P <0.05) with a significantly higher mean GA at delivery (37 vs 35.1, P <0.05). The mean BW was not significantly different between these 2 groups.

We conducted further analysis using data from all 4 groups to look at the overall impact of age and number of eggs retrieved on CPR and LBR. We found a progressive decrease in CPR and LBR with rising age (Figs. 1 and 2). There was a significant impact of maternal age on CPR and LBR, with a 9% decrease in both CPR (OR 0.91, 0.90-0.93, P <0.0001) and LBR (OR 0.91, 0.89-0.92, P <0.0001) with

Table 2. Delivery Outcomes of Patients

	Double Day 2 to 3 Embryo Transfer	Single Blastocyst Transfer	Double Blastocyst Transfer	*P* Value
Clinical pregnancy rate	1925 (42.5%)	38 (45.2%)	32 (42.9%)	0.487
Miscarriages (before 24 weeks)	355 (7.83%)	6 (7.14%)	7 (10.77%)	0.662
Stillbirths (after 24 weeks)	11 (0.24%)	0	0	NA
Total live birth	1540 (34.0%)	32 (38.1%)	24 (36.9%)	0.651
Singleton	1161 (75.4%)	32 (100%)	17 (70.6%)	
Total multiple pregnancies	379 (24.6%)	0	7 (29.2%)	
Twins	377 (24.5%)	0	7 (29.2%)	
Triplets	2 (0.1%)	0	0	

NA: Not applicable

Table 3. Neonatal Outcomes of Babies Delivered in KKH

	Double Day 2 to 3 Embryo Transfer	Single Blastocyst Transfer	Double Blastocyst Transfer	*P* Value
Total no. of transfers	4533	84	65	
Total no. of live births reported	1921	32	31	
Total no. of live births in KKH	1910	32	29	
Full-term delivery (37 weeks and above)	1251 (65.8%)	27 (84.4%)	25 (86.2%)	0.007
Mean GA at delivery	36.7 ± 2.8 (23 – 42)	37.2 ± 3.91 (24 – 40)	37.5 ± 1.02 (36 – 40)	0.225
Mean BW	2718.5 ± 1217.1	2855.8 ± 751.9	2708.1 ± 507.6	0.814
Singleton (n)	1144	32	17	
Full-term delivery (37 weeks and above)	955 (84.1%)	27 (84.4%)	15 (88.2%)	0.896
Mean GA at delivery	37.8 ± 2.16 (23 – 42)	37.2 ± 3.91 (24 – 40)	37.9 ± 1.1 (36 – 40)	0.264
Mean BW	2995.3 ± 1022	2855.8 ± 751.9	3040.6 ± 349.3	0.730
Multiple pregnancies (n)	757	-	12	
Full-term delivery (37 weeks and above)	289 (38.2%)	-	10 (83.3%)	0.001
Mean GA at delivery	35.1 ± 2.91 (23 – 41)	-	37 ± 0.6 (36 – 38)	0.027
Mean BW	2303.4 ± 1364.6	-	2264.8 ± 301.6	0.922

BW: Birth weight; GA: Gestational age; KKH: KK Women's and Children's Hospital

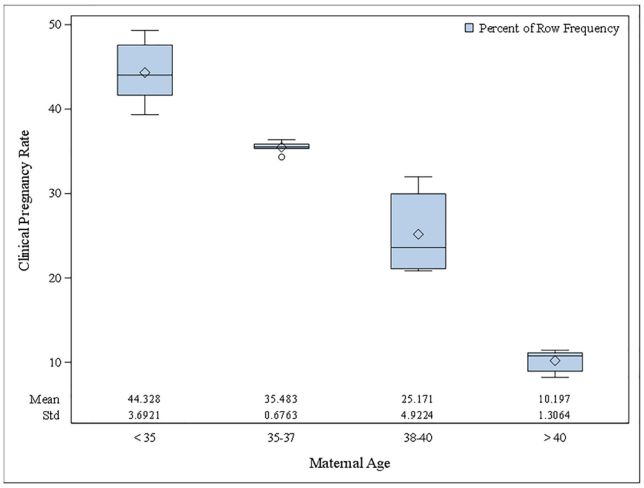

Fig. 1. Relationship between maternal age and clinical pregnancy rate.

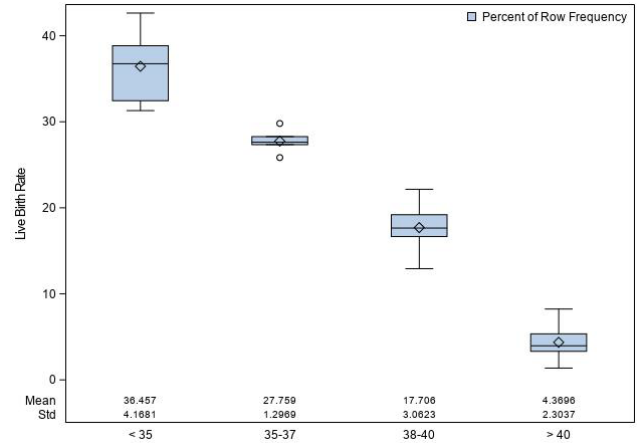

Fig. 2. Relationship between maternal age and live birth rate.

every year increase in age (Table 4). This is consistent with previous publications demonstrating the negative effect of maternal age on LBRs in ART.[7] Age is the single most important factor in determining success rates after IVF,[8] with success rates diminishing greatly after the age of 40.[9] In our study, there was a significant decrease in CPR with age. CPR decreased from 44.3% before 35 years of age to 10.2% after 40 years of age (Fig. 1). Similarly, LBR decreased from 36.5% before the age of 35 years to 4.4% after 40 years of age (Fig. 2).

We did not find any significant effects on the number of oocytes retrieved on CPR (OR 1.002, 0.995-1.01, *P* = 0.60) and LBR (OR 1.003, 0.996-1.01, *P* = 0.40) after adjusting for age (Table 4). Prior studies looking at the relationship between the number of eggs retrieved and LBR demonstrated a strong association (15 eggs retrieved being the optimal number).[10] However, such a relationship was not apparent in our study. This disparity in findings may have arisen from the exclusion of cancelled embryo transfers, which would have occurred more in those with lower number of oocytes retrieved.

Table 4. Effect of Age and Number of Oocytes Retrieved on Clinical Pregnancy Rate and Live Birth Rate (Adjusted for Age Using Multivariate Logistic Regression Analysis)

Effect	Clinical Pregnancy Rate		Live Birth Rate	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	0.91 (0.90, 0.93)	<0.0001	0.91 (0.89, 0.92)	<0.0001
Number of oocytes obtained	1.002 (0.995, 1.01)	0.6011	1.003 (0.996, 1.01)	0.4030

CI: Confidence interval; OR: Odds ratio

Based on our data, the LBR and CPR were significantly different among all 4 groups (P <0.001). Patients in the SET group were older patients with poorer ovarian response with a correspondingly lower number of oocytes retrieved, hence contributing to the significantly lower LBR and CPR. However, the LBR and CPR were not significantly different when we compare only the DET, single blastocysts stage embryo transfer and double blastocysts stage embryo transfer group (LBR: $P = 0.64$, CPR: $P = 0.48$). This is contrary to a previous study by Papanikolaou et al which demonstrated that blastocyst transfers have a higher LBR and CPR than cleavage-stage embryo transfers when the same number of embryos were transferred.[4] However, this result was not reproducible in other studies which also demonstrated no significant difference in pregnancy outcomes between blastocyst transfers and cleavage-stage embryo transfers.[11] We did not find any significant differences in CPR and LBR between DET and DBT groups despite the same number of embryos transferred. Moreover, we also noticed no difference in LBR and CPR in the single blastocysts stage embryo transfer group.

Previous studies pertaining to comparison between cleavage-stage embryo transfers and blastocyst transfers have yielded mixed results. The study by Schwarzler et al[12] showed that blastocyst transfers result in higher MPR with a significantly higher CPR, however, the study did not differentiate between double and SBTs. Based on our data, the patients who underwent SBT had a similar LBR as DBT, albeit with significantly fewer multiple pregnancies.

Conclusion

This retrospective review suggests that single blastocysts stage embryo transfer in a fresh IVF cycle has similar CPR and LBR as compared to DET and double blastocysts stage embryo transfer, without the complication of multiple pregnancies. The SET group had the poorest outcome, presumably due to the poor ovarian response and the lack of embryos to choose from for embryo transfer. However, our population of patients who underwent single blastocysts stage embryo transfer were younger and hence may inherently have a confounding effect on LBR. Hence, our data support the use of single blastocysts stage embryo transfer where patients are candidates for blastocyst culture to achieve an acceptable LBR and CPR while eliminating the risk of MPR and its attendant morbidities.

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Review Article

Identification and Measurement of Frailty: A Scoping Review of Published Research from Singapore

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Abstract

Introduction: The Asia-Pacific Clinical Practice Guidelines for the Management of Frailty recommended the use of validated measurement tools for identifying frailty. In an effort to contribute to the development of best practice guidelines in frailty identification and measurement, our scoping review aimed to present a summary of published research on this topic among older adults in Singapore. Our findings are important given the need to consider the context of use and the goals of measurement in using validated tools. Materials and Methods: We searched PubMed and CINAHL® for articles describing the identification and measurement of frailty among older adults (≥60 years) in Singapore and mined the bibliographies of eligible articles. An article was eligible if it involved empirical research on frailty using a structured frailty definition. We described such articles and the conceptual definitions they used, and summarised their operationalisation of frailty. Results: Our search yielded 165 records. After 2-stage screening of titles/abstracts and full-text articles, we retained 32 eligible articles for data extraction and thematic analysis. The extant literature in Singapore includes observational cross-sectional and longitudinal studies and intervention studies across community and tertiary care settings. Eligible articles commonly used the frailty phenotype and the deficit accumulation models in defining frailty, and reported measuring components of physical, cognitive, and/or social frailty. Conclusion: Our scoping review provided a broad evidence synthesis of the underpinnings of research on frailty identification and measurement in Singapore. Consistently applying standard methods and approaches in frailty identification and measurement can support evidence-based practice and policies in Singapore.

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Key words: Conceptual definitions, Evidence synthesis, Frailty research, Older adults

Introduction

Around a decade ago, frailty was an emerging research area and a nascent concept in many clinical specialties.[1] Today, its growing relevance in both research and clinical practice is sustained amid the ageing of populations across the world including Singapore. Ongoing initiatives in Singapore aim to equip the healthcare system with the capacity and infrastructure required for managing frailty in one of the most rapidly ageing populations;[2] such an endeavour warrants a consistent approach in identifying frailty.

Older adults with frailty have been broadly described in the international literature as "lacking in general strength and are unusually susceptible to disease or to other infirmity".[3] Until recently, frailty in older Singaporeans had been loosely applied to describe functionally dependent older adults[4] or a subgroup of hospitalised older patients.[5] A seminal review of international studies on the identification of frailty from 1997 to 2009 described an overview of clinical definitions, screening tools, and severity measures of frailty,[6] which guided subsequent research in the extant literature. Standard scientific inquiry and the growing importance of frailty measurement in clinical practice fuelled the initial development of the now commonly used conceptual models in defining frailty.[7,8] One such model described frailty as a clinical phenotype that consists of: 1) slow gait speed, 2) low physical activity, 3) shrinking,

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4) exhaustion, and 5) weakness; the presence of at least 3 of these attributes indicated frailty.[7] An alternative approach described a frailty index based on the accumulated number of clinically assessed deficits.[8-10] These early frameworks mainly pertained to the physical domain of frailty; more recent frameworks have considered the cognitive and social domains as well.[11]

The recently published Asia-Pacific Clinical Practice Guidelines for the Management of Frailty (AP-CPGMF) strongly recommended using a valid measurement tool in identifying frailty and emphasised the importance of adapting the guidelines to the local context.[12] Despite significant progress in developing comprehensive conceptual models, there is an apparent lack of consensus on the "component elements" of frailty.[6] This raises an important issue, because consistency in defining any construct is essential in obtaining valid and reliable measurements. Hence, a key step in guiding the selection of appropriate measures and applying a more consistent definition of frailty will require an overview of the scope of research on frailty identification and measurement in Singapore.

We conducted a scoping review of research involving the identification and measurement of frailty in Singapore to glean insights that can inform the selection of valid measurement tools for use in research and clinical settings, and enable the translation of relevant research into policy and practice. An overarching goal is to engage the local research community in frailty identification and measurement as well as stakeholders from the government and healthcare sectors. Specifically, we aimed to examine the following information from published studies in Singapore: a) characteristics of articles on frailty identification; b) definitions of frailty used; c) domains of frailty investigated; d) conceptual models applied to identify and measure frailty; e) corresponding component elements of frailty considered (i.e., indicators, factors, subdomains); and e) measurement tools used to identify frailty and/or determine its severity.

Materials and Methods

Published procedures for conducting scoping reviews guided our methodology.[13] Briefly, we identified the relevant articles, extracted data from the eligible ones, charted data using quantitative summaries and qualitative thematic synthesis, and examined the implications of the review findings for research, policy and practice.

Data Sources and Search Strategy

We searched PubMed and CINAHL® and performed reference mining of eligible articles to find additional relevant articles. We focused on empirical studies in Singapore that involved the identification and measurement of frailty among older adults. Our search strategy included database-indexed terms and equivalent free-text terms for the following key concepts: frailty, older adults, identification, and Singapore (Table 1). We did not apply any date and language limits or search filters in the database search (Appendix 1). Hence, the search results carried forward to the title and abstract screening stage included articles indexed in the databases up to the last date of search in May 2018. Even without applying language limits, the search did not generate articles published in a non-English language.

Study Selection and Data Extraction

Our review included articles that satisfied all of the following criteria: 1) reported empirical research based on primary and/or secondary data; 2) conducted in Singapore; 3) used data on older adults (i.e., sample mean ≥60 years or ≥1 participant aged ≥60 years); 4) specified the identification, measurement and/or assessment of frailty (i.e., measured frailty as a research variable); and 5) used a clear definition of frailty (i.e., a definition specific to the study or adapted from a frailty model). A clear definition of frailty is a key inclusion criterion given that frailty overlaps

Table 1. Overview of Search Strategy

Concept	Key Words
#1 Frailty	Frailty or frail or vulnerable or vulnerability
#2 Older adults	Aged or elderly
#3 Identification (definition, markers)	Risk factors
	Association
	Health status indicators
	Markers or biological markers or clinical markers
	Gait speed
	Physical activity
	Weight loss
	Cognitive impairment
	Depressive symptoms
	Exhaustion
	Weakness
	Hand grip strength
	Deficit or accumulation or cumulative
	Identification, assessment, measurement
#4 Identification (methods)	Health surveys
	Diagnosis
	Rating scales or index
	Risk assessment or case finding or geriatric assessment
	Disability evaluation
	Forecasting
	Patient care planning
#5 Singapore	Singapore

Search construction in databases: (#1 and #2) and (#3 or #4) and #5

with related concepts such as disability, weak hand grip strength, or weakness;[10,14] specifying this condition ensured that the articles included in our review considered frailty as a distinct concept.

We identified relevant articles through 2 stages of screening and 1 round of reference mining. In the first screening stage, each author screened the titles and abstracts of all articles from the search results independently using EndNote X7[15] reference manager and the Rayyan[16] web application for systematic reviews. In stage 2, each author further screened the full text of eligible titles and abstracts separately. We resolved conflicting assessments in the title and abstract screening (12 articles) through discussion; in the full-text screening (10 articles), the process mainly involved clarifying the definition of frailty. Finally, prior to data extraction, one author mined the reference lists of all eligible articles.

We obtained the full text of all eligible articles for data extraction. Key data extracted and summarised from the eligible articles include the basic study characteristics (e.g., first author name, publication year, primary aims, study design, etc.), and the following methodological information: a) frailty definition used; b) frailty domains examined (e.g., physical, cognitive, social, etc.); c) underlying conceptual approach specified or implied (e.g., phenotype, deficit accumulation, etc.); d) component elements of frailty measured (i.e., the factors, indicators, subdomains, which form or reflect the concept of frailty as defined in the underlying conceptual approach used in the article); e) operationalisation of the component elements; f) general scoring procedure and/or measurement cutoff values; g) frailty classification presented (e.g., frail, prefrail, non-frail); and h) references to the original conceptual models of frailty cited. We performed data extraction using EndNote X7 and MS Office Suite.

Data Synthesis

We described a quantitative summary of important study characteristics, which represents an overview of the recent developments in frailty identification research in Singapore. In addition, we put together a qualitative thematic analysis of the common definitions of frailty, as well as the conceptual models extensively used and adapted in published studies. We also teased out the salient variations in measuring various components of frailty.

Results

Our database search generated 165 records with 142 unique titles and abstracts (Fig. 1). After sequentially applying each inclusion criteria in the title and abstract screening, we excluded 88 articles that did not satisfy at least 1 criteria. We assessed the full text of the remaining 54 articles, of which we excluded 22 due to the lack of a clear definition of frailty or the omission of its operationalisation and measurement procedure. We finally identified 32 eligible articles for data extraction.

Characteristics of Eligible Articles

Table 2 describes the objectives and data sources, key variables examined, sample size, and study setting of the eligible articles, including the characteristics of the population of older adults they examined (i.e., age, disease condition, if specified). Although not mutually exclusive, the eligible articles measured frailty domains as independent or predictor variables (63%), or outcomes (44%). Several papers reported the relationship of frailty with respect to outcomes such as malnutrition,[17] mortality,[18,19] postsurgery outcomes,[20] healthcare utilisation,[21] and individual component elements of frailty such as walking/gait speed, functional status, and cognitive status.[22-24] A few papers investigated the impact of frailty transition on cognitive status[25] and the role of biological markers in frailty status and progression.[26] Studies that examined frailty transition/progression compared differences in frailty scores at baseline and 12 months later; an increase in frailty scores defined an increasing frailty state (progression).[25,26]

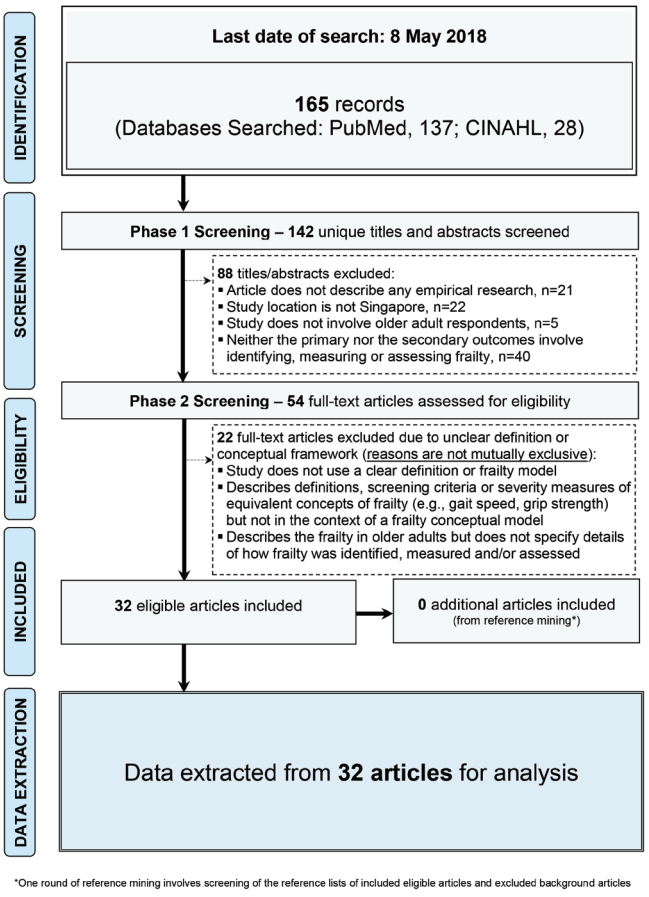

Fig. 1. Review flow diagram. Template from: Moher D. Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporing Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.doi:10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org.

Table 2. Characteristics of Articles Included in the Review, n = 32

Author (Year)	Study Objectives and Data Source*	Key Variables Examined	Sample Size	Study Setting† and Population Group	Age‡ (Years)	Frailty Model(s)
Longitudinal Design, n = 10						
Chong MS, et al (2015a)§	To study frailty transitions and change in cognitive status over 1-year follow-up among subjects with cognitive impairment	I/P: frailty transitions; D/O: cognitive status	122	(MCI or mild-moderate probable AD)	≥55	Buchman; Fried‖¶
Chia, et al (2016)#	To assess how a trans-institutional transdisciplinary programme was initiated incorporating seamless prehabilitation and rehabilitation to enhance the outcome further (postsurgery risk of morbidity)	I/P: frailty (risk stratification); D/O: postsurgery risk of morbidity	117	(Patients who received major colorectal resection)	(75 – 97)	Fried's criteria‖
Kua, et al (2016)**	To examine which frailty measure, Modified Fried Criteria and reported Edmonton frail scale, is a better predictor of early postoperative complications in a group of older hip fracture patients seen in the orthogeriatric service	I/P: frailty; D/O: postoperative complications	100	(Older adults admitted to the orthopaedic surgery unit)	≥60	Modified Fried Criteria; Edmonton Frail Scale‖††
Tay, et al (2016)‡‡	To examine the independent and combined effects of inflammation (IL-6 and TNF-α) and alterations in distinctly regulated endocrine axes on baseline frailty status and progressive physical frailty at 1 year, among older adults across a continuum of cognitive impairment	I/P: biological markers; D/O: frailty, frailty progression	99	Community-dwelling older adults with MCI and mild-moderate AD	≥55	Buchman; Fried‖¶

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

*Study-specific data were collected unless specified otherwise in brackets (Name of Dataset).

†Most articles reported community-based settings, tertiary care settings (i.e., tertiary hospitals) are enclosed in brackets ( ).

‡Most studies only reported inclusion criteria for age; if reported, the age range of participants are enclosed in brackets ( ).

§Chong MS, Tay L, Chan M, Lim WS, Ye R, Tan EK, et al. Prospective longitudinal study of frailty transitions in a community-dwelling cohort of older adults with cognitive impairment. BMC Geriatr 2015;15:175.

‖Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.

¶Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 2007;69:483-9.

#Chia CL, Mantoo SK, Tan KY. 'Start to finish trans-institutional transdisciplinary care': a novel approach improves colorectal surgical results in frail elderly patients. Colorectal Dis 2016;18:O43-50.

**Kua J, Ramason R, Rajamoney G, Chong MS. Which frailty measure is a good predictor of early post-operative complications in elderly hip fracture patients? Arch Orthop Trauma Surg 2016;136:639-47.

††Hilmer SN, Perera V, Mitchell S, Murnion BP, Dent J, Bajorek B, et al. The assessment of frailty in older people in acute care. Australas J Ageing 2009;28:182-8.

‡‡Tay L, Lim WS, Chan M, Ye RJ, Chong MS. The independent role of inflammation in physical frailty among older adults with mild cognitive impairment and mild-to-moderate Alzheimer's disease. J Nutr Health Aging 2016;20:288-99.

§§Chew J, Lim WS, Chong MS, Ding YY, Tay L. Impact of frailty and residual subsyndromal delirium on 1-year functional recovery: A prospective cohort study. Geriatr Gerontol Int 2017;17:2472-8.

‖‖Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci 2007;62:738-43.

¶¶Chong E, Ho E, Baldevarona-Llego J, Chan M, Wu L, Tay L. Frailty and risk of adverse outcomes in hospitalized older adults: a comparison of different frailty measures. J Am Med Dir Assoc 2017;18:638.e637-638.e611.

##Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-95.

***Tan KY, Kawamura YJ, Tokomitsu A, Tang T. Assessment for frailty is useful for predicting morbidity in elderly patients undergoing colorectal cancer resection whose comorbidities are already optimized. Am J Surg 2017;204:139-43.

†††Chong E, Chan M, Lim WS, Ding YY. Frailty predicts incident urinary incontinence among hospitalized older adults – a 1-year prospective cohort study. J Am Med Dir Assoc 2018;19:422-7.

‡‡‡Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012;16:601-8.

§§§Chong E, Ho E, Baldevarona-Llego J, Chan M, Wu L, Tay L, et al. Frailty in hospitalized older adults: comparing different frailty measures in predicting short- and long-term patient outcomes. J Am Med Dir Assoc 2018;19:450-7.e3.

‡‡‡‡Lu Y, Tan CT, Nyunt MS, Mok EW, Camous X, Kared H, et al. Inflammatory and immune markers associated with physical frailty syndrome: findings from Singapore longitudinal aging studies. Oncotarget 2016;7:28783-95.
§§§§Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr 2002;2:1.
‖‖‖‖Merchant RA, Banerji S, Singh G, Chew E, Poh CL, Tapawan SC, et al. Is trunk posture in walking a better marker than gait speed in predicting decline in function and subsequent frailty? J Am Med Dir Assoc 2016;17:65-70.
####Merchant RA, Chen MZ, Tan LWL, Lim MY, Ho HK, van Dam RM, et al. Singapore Healthy Older People Everyday (HOPE) study: prevalence of frailty and associated factors in older adults. J Am Med Dir Assoc 2017;18:734.e9-734.e14.
**** *Nyunt MSZ, Soh CY, Gao Q, Gwee X, Ling ASL, Lim WS, et al. Characterisation of physical frailty and associated physical and functional impairments in mild cognitive impairment. Front Med (Lausanne) 2017;4:230.
††††Vaingankar JA, Chong SA, Abdin E, Picco L, Chua BY, Shafie S, et al. Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. Geriatr Gerontol Int 2017;17:1444-54.
‡‡‡‡Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Frailty and malnutrition: related and distinct syndrome prevalence and association among community-dwelling older adults: Singapore Longitudinal Ageing Studies. J Am Med Dir Assoc 2017;18:1019-28.
§§§§Yash Pal R, Kuan WS, Koh Y, Venugopal K, Ibrahim I. Death among elderly patients in the emergency department: a needs assessment for end-of-life care. Singapore Med J 2017;58:129-33.
‖‖‖‖Lunney JR, Lynn J, Hogan C. Profiles of older medicare decedents. J Am Geriatr Soc 2002;50:1108-12.
¶¶¶¶Chye L, Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Strong relationship between malnutrition and cognitive frailty in the Singapore Longitudinal Ageing Studies (SLAS-1 and SLAS-2). J Prev Alzheimers Dis 2018;5:142-8.
#####Ge L, Yap CW, Heng BH. Prevalence of frailty and its association with depressive symptoms among older adults in Singapore. Aging Ment Health 2018:1-6.
******Pannérec A, Migliavacca E, De Castro A, Michaud J, Karaz S, Goulet L, et al. Vitamin B12 deficiency and impaired expression of amnionless during aging. J Cachexia Sarcopenia Muscle 2018;9:41-52.
†††††Tan LF, Lim ZY, Choe R, Seetharaman S, Merchant R. Screening for frailty and sarcopenia among older persons in medical outpatient clinics and its associations with healthcare burden. J Am Med Dir Assoc 2017;18:583-7.
‡‡‡‡‡Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35:526-9.
§§§§§Feng L, Nyunt MS, Feng L, Yap KB, Ng TP. Frailty predicts new and persistent depressive symptoms among community-dwelling older adults: findings from Singapore Longitudinal Aging Study. J Am Med Dir Assoc 2014;15:76.e7-76.e12.
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¶¶¶¶¶Feng L, Zin Nyunt MS, Gao Q, Feng L, Yap KB, Ng TP. Cognitive frailty and adverse health outcomes: findings from the Singapore Longitudinal Ageing Studies (SLAS). J Am Med Dir Assoc 2017;18:252-8.
######Teo N, Gao Q, Nyunt MSZ, Wee SL, Ng TP. Social frailty and functional disability: findings from the Singapore Longitudinal Ageing Studies. J Am Med Dir Assoc 2017;18:637.e13-637.e19.
*******Kwok BC, Pua YH, Mamun K, Wong WP. The minimal clinically important difference of six-minute walk in Asian older adults. BMC Geriatr 2013;13:23.
††††††Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85-94.
‡‡‡‡‡‡Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. Am J Med 2015;128:1225-36.e1221.
§§§§§§Ng TP, Nyunt MSZ, Feng L, Feng L, Niti M, Tan BY, et al. Multi-domains lifestyle interventions reduces depressive symptoms among frail and pre-frail older persons: randomized controlled trial. J Nutr Health Aging 2017;21:918-26.

Table 2. Characteristics of Articles Included in the Review, n = 32 (Cont'd)

Author (Year)	Study Objectives and Data Source*	Key Variables Examined	Sample Size	Study Setting† and Population Group	Age‡ (Years)	Frailty Model(s)
Chew, et al (2017)§§	To investigate the association of frailty with incomplete delirium recovery at discharge (i.e., residual subsyndromal delirium) and examine its mediating role in the relationship between frailty and functional recovery at 12 months postdelirium	I/P: frailty; D/O: functional recovery	234	(Patients admitted to the geriatrics unit)	≥65	Rockwood Frailty Index‖‖
Chong E, et al (2017)¶¶	To: 1) compare the performance of frailty measures: fatigue, resistance, ambulation, illnesses, and loss of weight, FRAIL scale; Tilburg Frailty Indicator; and Clinical Frailty Scale using the widely adopted Frailty Index as gold standard, and 2) compare their ability to predict negative outcomes in hospitalised older adults	I/P: frailty; diagnostic performance of frailty measures; D/O: in-hospital mortality, length of stay, institutionalisation, functional decline	210	(Patients admitted to the department of geriatric medicine)	≥65	RockwoodClinical Frailty Scale##

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

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‖Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.

¶Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 2007;69:483-9.

[#]Chia CL, Mantoo SK, Tan KY. 'Start to finish trans-institutional transdisciplinary care': a novel approach improves colorectal surgical results in frail elderly patients. Colorectal Dis 2016;18:O43-50.
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[††]Hilmer SN, Perera V, Mitchell S, Murnion BP, Dent J, Bajorek B, et al. The assessment of frailty in older people in acute care. Australas J Ageing 2009;28:182-8.
[‡‡]Tay L, Lim WS, Chan M, Ye RJ, Chong MS. The independent role of inflammation in physical frailty among older adults with mild cognitive impairment and mild-to-moderate Alzheimer's disease. J Nutr Health Aging 2016;20:288-99.
[§§]Chew J, Lim WS, Chong MS, Ding YY, Tay L. Impact of frailty and residual subsyndromal delirium on 1-year functional recovery: A prospective cohort study. Geriatr Gerontol Int 2017;17:2472-8.
[||]Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci 2007;62:738-43.
[¶¶]Chong E, Ho E, Baldevarona-Llego J, Chan M, Wu L, Tay L. Frailty and risk of adverse outcomes in hospitalized older adults: a comparison of different frailty measures. J Am Med Dir Assoc 2017;18:638.e637-638.e611.
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[*****]Nyunt MSZ, Soh CY, Gao Q, Gwee X, Ling ASL, Lim WS, et al. Characterisation of physical frailty and associated physical and functional impairments in mild cognitive impairment. Front Med (Lausanne) 2017;4:230.
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[‡‡‡‡‡]Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Frailty and malnutrition: related and distinct syndrome prevalence and association among community-dwelling older adults: Singapore Longitudinal Ageing Studies. J Am Med Dir Assoc 2017;18:1019-28.
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Author (Year)	Study Objectives and Data Source*	Key Variables Examined	Sample Size	Study Setting† and Population Group	Age‡ (Years)	Frailty Model(s)
Tan KY, et al (2017)[***]	To examine whether frailty is useful in predicting adverse outcomes in optimised elective older colorectal surgery patients	I/P: frailty; D/O: postsurgery outcomes, mortality	83	(Patients for elective colorectal resection)	(75 – 93)	Fried's criteria[‖]
Chong E, et al (2018a)[†††]	To examine the ability of frailty to predict incident urinary incontinence in hospitalised older adults	I/P: frailty; D/O: urinary incontinence	210	(Patients admitted to the geriatrics unit)	≥65	Morley FRAIL scale[‡‡‡]
Chong E, et al (2018b)[§§§]	To compare the diagnostic performance of the FRAIL scale, Clinical Frailty Scale, and Tilburg Frailty Indicator and their ability to predict negative outcomes 12 months after enrolment	I/P: diagnostic performance of measures; D/O: mortality, length of stay, institutionalisation, functional decline	210	(Patients admitted to the geriatric medicine unit)	≥65	RockwoodClinical Frailty Scale[###]
Tan QL, et al (2018)[‖‖]	To examine the feasibility and effects of conducting a 12-week structured Functional Power Training programme in a housing estate	I/P: programme evaluation; D/O: functional outcomes, frailty	9	Community-dwelling older adults	≥55	Morley FRAIL scale[‡‡‡]

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

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‡‡‡‡Lu Y, Tan CT, Nyunt MS, Mok EW, Camous X, Kared H, et al. Inflammatory and immune markers associated with physical frailty syndrome: findings from Singapore longitudinal aging studies. Oncotarget 2016;7:28783-95.

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Author (Year)	Study Objectives and Data Source*	Key Variables Examined	Sample Size	Study Setting† and Population Group	Age‡ (Years)	Frailty Model(s)
Cross-Sectional Design, n = 15						
Chong MS, et al (2014)[¶¶¶]	To explore if there are stage-specific differences in the relationship between frailty and cognitive impairment	I/P: frailty; D/O: cognitive impairment	122	MCI and mild-moderate probable AD	≥55	Buchman; Fried[¶]
Ng, et al (2014)[###]	To develop a frailty risk prediction tool based on simple and routine clinical measurements and validated it for use in primary care using data from cohorts of community-living older adults (SLAS-2)	I/P: clinical measurements; D/O: frailty	1685	Community-dwelling older adults	≥55	Fried's criteria[§]

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

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Chong MS, et al (2015b)[****]	To explore factors associated with frailty across the continuum of healthy ageing to cognitive impairment (MCI, mild and moderate AD) (GERILABS)	I/P: cognitive, functional characteristics; D/O: frailty	299	Community-dwelling	≥50	Buchman; Fried[¶]
Ng, et al (2015a)[††††]	To explore the association of specific subsets of markers of immune senescence and the immune risk profile with frailty (SLAS-2)	I/P: biological markers; D/O: frailty	421	Community-dwelling older adults	≥55	Fried's criteria[l]
Lu, et al (2016)[‡‡‡‡]	To identify frailty-related inflammatory markers and immunological phenotypes in a cohort of community-dwelling adults	I/P: biological markers; D/O: frailty	76	Community-dwelling older Chinese adults	≥55	Fried; Mitnitski[§§§§]

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

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Table 2. Characteristics of Articles Included in the Review, n = 32 (Cont'd)

Author (Year)	Study Objectives and Data Source*	Key Variables Examined	Sample Size	Study Setting† and Population Group	Age‡ (Years)	Frailty Model(s)
Merchant, et al (2016)¶¶¶¶	To identify early adaptations in posture in walking preceding actual decline in gait speed among healthy Chinese men	I/P: walking posture; D/O: gait speed	90	Community-dwelling Chinese men	(60 – 80)	Rockwood Clinical Frailty Scale##
Merchant, et al (2017)####	To investigate the prevalence of frail and prefrail states and their association with polypharmacy, multimorbidity, cognitive and functional status, and perceived health status among community-dwelling older adults in Singapore (HOPE)	I/P: frailty/prefrailty; D/O: frailty; health-related outcomes	1051	Community-dwelling older adults from northwest Singapore	≥65	Morley FRAIL scale[36]
Nyunt, et al (2017)*****	To characterise the physical frailty phenotype and its associated physical and functional impairments in MCI (SLAS-2)	I/P: physical and functional impairments; D/O: frailty	1938	Community-dwelling older adults	≥55	Fried's criteria¶

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

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Wei, et al (2017)‡‡‡‡‡	To investigate the prevalence of prefrailty/frailty and nutritional risk; their overlapping prevalence; compare sociodemographic, physical, and mental health risk factors and their association independent of other factors (SLAS)	I/P: sociodemographic, clinical factors; D/O: frailty, nutritional risk	6045	Community-dwelling older adults	(55 – 98)	Fried's criteria[l]
Yash Pal, et al (2017)§§§§§	To determine the incidence and nature of death among patients aged ≥65 years in an emergency department; describe trajectories of death	I/P: frailty; D/O: incidence, trajectories of death	197	(Patients in emergency department)	≥65	Lunney¶¶¶¶

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

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Table 2. Characteristics of Articles Included in the Review, n = 32 (Cont'd)

Author (Year)	Study Objectives and Data Source*	Key Variables Examined	Sample Size	Study Setting† and Population Group	Age‡ (Years)	Frailty Model(s)
Chye, et al (2018)¶¶¶	To examine the prevalence of malnutrition among older adults in the Singapore Longitudinal Ageing Study cohort by their physical frailty and cognitive status (SLAS-1 and SLAS-2)	I/P: frailty, cognitive status; D/O: malnutrition	5414	Two cohorts of a population-based study of community dwelling older adults	≥55	Fried's criteria[l]
Ge, et al (2018)#####	To: 1) estimate the prevalence of frailty among community-dwelling older adults, and 2) investigate the independent association between level of frailty and depressive symptoms (PHI)	I/P: frailty; D/O: frailty; depressive symptoms	1942	Community-dwelling adults	≥60	Rockwood Clinical Frailty Scale[##]
Pannerec, et al (2018)******	To examine whether ageing and frailty associate with altered vitamin B12 homeostasis in humans and investigated the underlying molecular mechanisms using preclinical models (SLAS)	I/P: vitamin B12 homeostasis; D/O: ageing, frailty	238	Community-dwelling older adults	≥55	Fried's criteria[l]
Tan LF, et al (2018)††††††	To examine whether the Sarcopenia-frailty and Edmonton frail screening tools are clinically useful in identifying patients at risk for negative health outcomes who would benefit from intervention	I/P: frailty (screening tools); D/O: risk of negative outcomes	115	(Older adults attending specialist outpatient clinics)	≥65	Rolfson; Edmonton Frail Scale‡‡‡‡‡‡

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

*Study-specific data were collected unless specified otherwise in brackets (Name of Dataset).

†Most articles reported community-based settings, tertiary care settings (i.e., tertiary hospitals) are enclosed in brackets ( ).

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#Chia CL, Mantoo SK, Tan KY. 'Start to finish trans-institutional transdisciplinary care': a novel approach improves colorectal surgical results in frail elderly patients. Colorectal Dis 2016;18:O43-50.

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††Hilmer SN, Perera V, Mitchell S, Murnion BP, Dent J, Bajorek B, et al. The assessment of frailty in older people in acute care. Australas J Ageing 2009;28:182-8.

‡‡Tay L, Lim WS, Chan M, Ye RJ, Chong MS. The independent role of inflammation in physical frailty among older adults with mild cognitive impairment and mild-to-moderate Alzheimer's disease. J Nutr Health Aging 2016;20:288-99.

§§Chew J, Lim WS, Chong MS, Ding YY, Tay L. Impact of frailty and residual subsyndromal delirium on 1-year functional recovery: A prospective cohort study. Geriatr Gerontol Int 2017;17:2472-8.

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##Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-95.

***Tan KY, Kawamura YJ, Tokomitsu A, Tang T. Assessment for frailty is useful for predicting morbidity in elderly patients undergoing colorectal cancer resection whose comorbidities are already optimized. Am J Surg 2017;204:139-43.

†††Chong E, Chan M, Lim WS, Ding YY. Frailty predicts incident urinary incontinence among hospitalized older adults – a 1-year prospective cohort study. J Am Med Dir Assoc 2018;19:422-7.

‡‡‡Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012;16:601-8.

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‖‖Tan QLL, Chye LMY, Ng DHM, Chong MS, Ng TP, Wee SL. Feasibility of a community-based functional power training program for older adults. Clin Interv Aging 2018;13:309-16.

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[*****]Nyunt MSZ, Soh CY, Gao Q, Gwee X, Ling ASL, Lim WS, et al. Characterisation of physical frailty and associated physical and functional impairments in mild cognitive impairment. Front Med (Lausanne) 2017;4:230.
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[**********]Ge L, Yap CW, Heng BH. Prevalence of frailty and its association with depressive symptoms among older adults in Singapore. Aging Ment Health 2018:1-6.
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Author (Year)	Study Objectives and Data Source*	Key Variables Examined	Sample Size	Study Setting† and Population Group	Age‡ (Years)	Frailty Model(s)
Combination of Cross-Sectional and Longitudinal Design, n = 4						
Feng, et al (2014)[§§§§§§]	This study aimed to examine the cross-sectional and longitudinal relationships between physical frailty at baseline and depressive symptoms at baseline and at follow-up (SLAS-1)	I/P: frailty; D/O: depressive symptoms	1827	Community-dwelling older Chinese adults	≥55	Fried's criteria[l]
Feng, et al (2017a)[¶¶¶¶¶¶]	To test the following hypotheses: 1) physical frailty is associated with a higher likelihood of prevalent cognitive impairment, 2) physical frailty and cognitive impairment independently predict an increased risk of incident MCI and dementia, and 3) cognitive frailty markedly increases the risks of developing NCD (SLAS-1)	I/P: frailty; D/O: cognitive impairment; risk of MCI and dementia; risk of developing NCDs	1575	Community-dwelling older Chinese adults	≥55	Fried's criteria[l]
Feng, et al (2017b)[########]	To determine whether concurrent physical frailty and cognitive impairment, compared with physical frailty alone, substantially increased the risk of mortality, functional disability, hospitalisation, and impaired quality of life (SLAS-1)	I/P: frailty, cognitive impairment; D/O: risk of mortality, disability, hospitalisation, impaired quality of life	2375	Community-dwelling older Chinese adults	≥55	Fried's criteria[l]

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

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Teo, et al (2017)[######]	To examine the association between the social frailty (SF) phenotype and functional disability, independent of the physical frailty (PF) phenotype, and compare the abilities of the PF, SF, and combined SF and PF indexes for predicting functional disability (SLAS-1)	I/P: frailty; D/O: functional disability	2406	Community-dwelling older adults	≥55	Fried's criteria[l]
Intervention Design (Randomised Controlled Trial), n = 3						
Kwok, et al (2013)[*******]	To examine the minimal clinically important difference for the 6-minute walk distance among frail Asian older adults (EFFECT)	I/P: frailty; D/O: 6-minute walking distance	73	Community-dwelling older adults with fear of falling	70, mean	Guralnik[†††††††]
Ng, et al (2015b)[‡‡‡‡‡‡‡]	To compare the effects of 6-month interventions with physical exercise, nutritional supplementation, cognitive training, and a combination of these with usual care control in reducing frailty	I/P: effects of intervention programme; D/O: reduced frailty	246	Community residents in the southwest region of Singapore	≥65	Fried's criteria[l]
Ng, et al (2017)[§§§§§§§]	To examine the effects of multiple-domain lifestyle interventions among older persons in reducing depressive symptoms; association of changes in frailty outcome with changes in depression outcomes	I/P: effects of intervention programme; D/O: frailty; depressive symptoms	246	Community-dwelling older adults	≥65	Fried's criteria[l]

AD: Alzheimer's disease; D/O: Dependent/outcome variable; EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; GERILABS: Longitudinal Assessment of Biomarkers for characterisation of early sarcopenia and predicting frailty and functional decline in community-dwelling Asian older adults study; HOPE: Healthy Older People Everyday Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); I/P, independent/predictor variable; MCI: Mild cognitive impairment; NCD: Neurocognitive disorder; PHI: Population Health Index (survey conducted in the Central Region of Singapore); SLAS: Singapore Longitudinal Ageing Study; WISE: Well-being of the Singapore Elderly

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[§]Chong MS, Tay L, Chan M, Lim WS, Ye R, Tan EK, et al. Prospective longitudinal study of frailty transitions in a community-dwelling cohort of older adults with cognitive impairment. BMC Geriatr 2015;15:175.

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[¶]Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 2007;69:483-9.

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§§§§Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr 2002;2:1.
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**********Nyunt MSZ, Soh CY, Gao Q, Gwee X, Ling ASL, Lim WS, et al. Characterisation of physical frailty and associated physical and functional impairments in mild cognitive impairment. Front Med (Lausanne) 2017;4:230.
††††††Vaingankar JA, Chong SA, Abdin E, Picco L, Chua BY, Shafie S, et al. Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. Geriatr Gerontol Int 2017;17:1444-54.
‡‡‡‡Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Frailty and malnutrition: related and distinct syndrome prevalence and association among community-dwelling older adults: Singapore Longitudinal Ageing Studies. J Am Med Dir Assoc 2017;18:1019-28.
§§§§Yash Pal R, Kuan WS, Koh Y, Venugopal K, Ibrahim I. Death among elderly patients in the emergency department: a needs assessment for end-of-life care. Singapore Med J 2017;58:129-33.
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¶¶¶¶Chye L, Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Strong relationship between malnutrition and cognitive frailty in the Singapore Longitudinal Ageing Studies (SLAS-1 and SLAS-2). J Prev Alzheimers Dis 2018;5:142-8.
########Ge L, Yap CW, Heng BH. Prevalence of frailty and its association with depressive symptoms among older adults in Singapore. Aging Ment Health 2018:1-6.
**********Panneerec A, Migliavacca E, De Castro A, Michaud J, Karaz S, Goulet L, et al. Vitamin B12 deficiency and impaired expression of amnionless during aging. J Cachexia Sarcopenia Muscle 2018;9:41-52.
††††††Tan LF, Lim ZY, Choe R, Seetharaman S, Merchant R. Screening for frailty and sarcopenia among older persons in medical outpatient clinics and its associations with healthcare burden. J Am Med Dir Assoc 2017;18:583-7.
‡‡‡‡‡‡Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35:526-9.
§§§§§Feng L, Nyunt MS, Feng L, Yap KB, Ng TP. Frailty predicts new and persistent depressive symptoms among community-dwelling older adults: findings from Singapore Longitudinal Aging Study. J Am Med Dir Assoc 2014;15:76.e7-76.e12.
¶¶¶¶Feng L, Nyunt MS, Gao Q, Feng L, Lee TS, Tsoi T, et al. Physical frailty, cognitive impairment, and the risk of neurocognitive disorder in the Singapore Longitudinal Ageing Studies. J Gerontol A Biol Sci Med Sci 2017;72:369-75.
¶¶¶¶¶Feng L, Zin Nyunt MS, Gao Q, Feng L, Yap KB, Ng TP. Cognitive frailty and adverse health outcomes: findings from the Singapore Longitudinal Ageing Studies (SLAS). J Am Med Dir Assoc 2017;18:252-8.
########Teo N, Gao Q, Nyunt MSZ, Wee SL, Ng TP. Social frailty and functional disability: findings from the Singapore Longitudinal Ageing Studies. J Am Med Dir Assoc 2017;18:637.e13-637.e19.
**********Kwok BC, Pua YH, Mamun K, Wong WP. The minimal clinically important difference of six-minute walk in Asian older adults. BMC Geriatr 2013;13:23.
††††††Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85-94.
‡‡‡‡‡‡Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. Am J Med 2015;128:1225-36.e1221.
§§§§§§Ng TP, Nyunt MSZ, Feng L, Feng L, Niti M, Tan BY, et al. Multi-domains lifestyle interventions reduces depressive symptoms among frail and pre-frail older persons: randomized controlled trial. J Nutr Health Aging 2017;21:918-26.

Our quantitative summary (Fig. 2) shows that the number of relevant publications on frailty identification in Singapore has substantially increased over the last 5 years. Although the majority of publications reported using study-specific data (53%), a substantial proportion (31%) used data from the Singapore Longitudinal Ageing Studies.[17,22,27-34] The majority of papers reported investigations in the community setting (68%). Finally, published works in Singapore largely involved observational cross-sectional (47%) and longitudinal studies (31%), with a few randomised controlled trials (9%).

Frailty Domains and Definitions

Among the frailty domains of current interest, physical frailty has been the most widely investigated (72%) in Singapore; the remainder of articles presented investigations on physical frailty in combination with at least 1 other domain (i.e., cognitive, social, and psychological frailty). Table 3 summarises the commonly adopted definitions of frailty per domain in the local literature.

Components of Frailty: Conceptual Models and Operationalisation

Table 4 presents a synopsis of the conceptual models used in the eligible articles, including the operationalisation and measurement of the frailty components investigated therein. The eligible articles were largely based on the frailty phenotype (e.g., Fried criteria,[7] Buchman's composite measure,[35] FRAIL [Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight] scale[36]) and the deficit accumulation model (e.g., Rockwood,[9] Mitnitski[8]). Some studies used Fried's frailty phenotype with a number of modifications.[28,30,31] Individual studies used each of these frameworks alone or in combination (e.g., physical frailty phenotype combined with models measuring cognitive[37] and psychosocial[38] frailty).

In organising the conceptual models, we noted substantial variations in the physical frailty components measured even among the articles that shared the same conceptual basis.[23,39,40] For example, Fried's criteria originally used "shrinking, weakness, exhaustion, slowness, and low activity" to describe the characteristics of frailty.[7] A number of articles[22,27,40,41] directly applied Fried's criteria in their investigations. Other studies[18,39] based on Fried's criteria used "weight loss, grip strength, exhaustion, walking speed, and physical activity", which deviate from the original nomenclature of frailty components but are nonetheless related. Frailty components considered in studies based on deficit models (i.e., frailty index)[42-44] included items that are commonly available in comprehensive geriatric assessments, such as the number of chronic diseases, functional performance, laboratory markers, strength, and

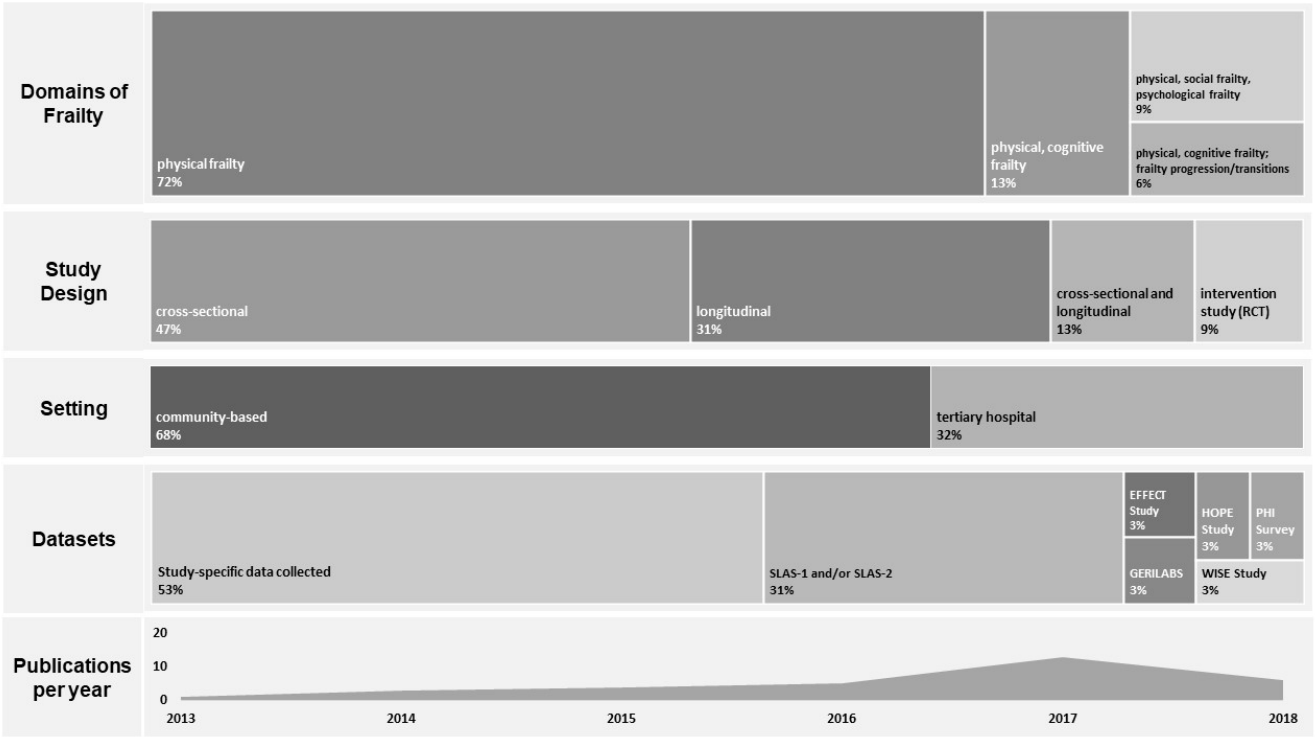

Fig. 2. Chart showing the eligible articles at a glance (n = 32). EFFECT: Evaluation of the Frails' Fall Efficacy by Comparing Treatments Study; GERILABS: Longitudinal Assessment of Biomarkers for Characterisation of Early Sarcopenia and Predicting Frailty and Functional Decline in Community-Dwelling Asian Older Adults Study; HOPE: Healthy Older People Every day Study (embedded in the Singapore Population Health Studies cohort Bukit Panjang); PHI: Population Health Index survey; SLAS-1 and 2: Singapore Longitudinal Ageing Studies (Waves 1 and 2); WISE: Well-being of the Singapore Elderly

Table 3. Common Definitions of Frailty in the Reviewed Articles

Definitions*	Conceptual Model	Domains Covered
A physical phenotype comprising criteria of shrinking, weakness, exhaustion, slowness, and low physical activities.†	Frailty phenotype	Physical frailty
A continuous composite measure of frailty consisting of grip strength, timed walk, body composition, and fatigue.‡	Frailty phenotype	Physical frailty
Frailty phenotype based on self-report: fatigue, resistance, ambulation, illness, and loss of weight.§	Frailty phenotype	Physical frailty
The simultaneous presence of both physical frailty and cognitive impairment without concurrent dementia or other dementias.‖,¶,#,**	None	Physical, cognitive frailty
A multifaceted concept that involves a continuum of being at risk of losing, or having lost general or social resources, social behaviours and activities, and self-management abilities that are important for fulfilling basic social needs.††	None	Social frailty
Diminished strength, physiologic malfunctioning leading to increased vulnerability to minor stressors that ultimately results in adverse health outcomes.§	Index of deficit accumulation	Physical frailty
The cycle of frailty indicates reduced levels of nutrition and activity, age-related musculoskeletal changes, and disease as being the possible precursors to loss of muscle mass as seen in the onset of sarcopenia, which progressed to decreased walking speed, strength, and power along with respiratory and metabolic changes.‡‡	Index of deficit accumulation	Physical frailty
A syndrome with multiple reduced physiologic functions that increases an individual's vulnerability for developing increased dependency and/or death.§§	Index of deficit accumulation	Physical, social frailty
A non-specific state of impaired strength, endurance, and balance; vulnerability to trauma and stressors; and high risk for morbidity, disability, mortality and institutionalisation; identification of biomarkers associated with developing frailty.‖‖	Index of deficit accumulation	Physical, social frailty
A state of decreased functional reserve and resistance to stressors that are associated with a high prevalence of adverse health outcomes, such as poor functional and cognitive status, falls, institutionalisation, and mortality.¶¶	Index of deficit accumulation	Physical, cognitive, social frailty

*These definitions were either used or adapted by the reviewed articles (i.e., studies conducted in Singapore). The citations may refer to the articles included in the review or the original studies cited in these articles.

†Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.

‡Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 2007;69:483-9.

§Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012;16:601-8.

‖Chye L, Wei K, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Strong relationship between malnutrition and cognitive frailty in the Singapore Longitudinal Ageing Studies (SLAS-1 and SLAS-2). J Prev Alzheimers Dis 2018;5:142-8.

¶Feng L, Zin Nyunt MS, Gao Q, Feng L, Yap KB, Ng TP. Cognitive frailty and adverse health outcomes: findings from the Singapore Longitudinal Ageing Studies (SLAS). J Am Med Dir Assoc 2017;18:252-8.

#Feng L, Nyunt MS, Gao Q, Feng L, Lee TS, Tsoi T, et al. Physical frailty, cognitive impairment, and the risk of neurocognitive disorder in the Singapore Longitudinal Ageing Studies. J Gerontol A Biol Sci Med Sci 2017;72:369-75.

**Merchant RA, Chen MZ, Tan LWL, Lim MY, Ho HK, van Dam RM, et al. Singapore Healthy Older People Everyday (HOPE) study: prevalence of frailty and associated factors in older adults. J Am Med Dir Assoc 2017;18:734.e9-734.e14.

††Bunt S, Steverink N, Olthof J, van der Schans CP, Hobbelen JSM. Social frailty in older adults: a scoping review. Eur J Ageing 2017;14:323-34.

‡‡Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-95.

§§Hilmer SN, Perera V, Mitchell S, Murnion BP, Dent J, Bajorek B, et al. The assessment of frailty in older people in acute care. Australas J Ageing 2009;28:182-8.

‖‖Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr 2002;2:1.

¶¶Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton Frail Scale. Age Ageing 2006;35:526-9.

gait characteristics, to name a few. Studies that examined the cognitive and psychosocial domains of frailty[17,22,26,32,33,45,46] measured cognitive impairment and sociodemographic data, respectively, as their relevant frailty components.

The operationalisation of frailty components also varied across the eligible articles. For instance, different studies defined shrinking/weight loss as unintentionally losing ≥4.5 kilogrammes in the last 3 months,[40] 6 months,[22] or 12 months.[18] Similarly, several studies defined weakness by measuring hand grip strength[24-26,45] or knee extension strength.[22,23,29,41]

Procedures for calculating frailty scores were relatively more consistent. In general, investigations that used the frailty phenotype deemed frailty as the presence of 3 out of 5 components. Alternatively, a frailty index score of 0.25 denotes frailty based on the deficit accumulation model.[42] Studies that investigated cognitive frailty used a standard test for cognitive impairment (i.e., Mini Mental State Examination [MMSE]) to operationalise cognitive frailty.[17,32,33,46] Cutoff scores for cognitive frailty across several papers ranged from ≤26 to ≤23 in the MMSE. The social frailty index (range 0-7), is based on the presence

Table 4. Conceptual Models of Frailty Identification and Measurement in the Reviewed Articles

Index Reference*	Reviewed Articles	Frailty Components	Operationalisation, Scoring, and Categories of Frailty
Physical Frailty – Frailty Phenotype			
Guralnik (1994)‡	Kwok, et al (2013)§	• Moderate frailty	• Assessed based on established guidelines for instructions • Cutoff: scored 5 to 9 (Short Physical Performance Battery is considered moderate frailty)
Fried (2001)‖	Feng, et al (2014)¶	• Shrinking • Slowness • Weakness • Exhaustion • Low activity	Modifications to Fried's criteria: • Low activity: score below the lowest sex-adjusted quintile of the total • Cutoff: score 1 for each component present; Frail = 3 to 5 points; prefrail = 1 to 2; non-frail = 0 • Categories: frail, prefrail, non-frail
	Ng, et al (2014);# Ng, et al (2015);** Pannerec, et al (2018)††	• Shrinking • Slowness • Weakness • Exhaustion • Low activity	Modifications to Fried's criteria: • Low activity (physical activities): self-reported hours spent doing light, moderate, vigorous activities; total amount of time spent on moderate and vigorous activities per week; activity time below the gender-specific lowest quintile (low activity) • Cutoff: score 1 point for each component present; frail = 3 to 5 points; prefrail = 1 to 2; robust = 0 • Categories: frail, prefrail, robust
	Ng, et al (2015);‡‡ Ng, et al (2017);§§ Nyunt, et al (2017)‖‖	• Shrinking • Slowness • Weakness • Exhaustion • Low activity	• Shrinking: BMI of 18.5 kg/m^2 and/or unintentional weight loss ≥10 pounds in the last 6 months • Slowness (6-minute fast gait speed test): lowest quintile values stratified for gender and height • Weakness (leg muscle strength using dominant knee extension): in lowest quintiles • Exhaustion: score of <10; total (range 3 to15); "Did you feel – worn out/tired/ have a lot of energy" • Low activity: average minutes per day spent on physical activities; lowest quintile is classified as low activity • Cutoff: 1 = present, 0 = absent; total score 0 to 5; frail = 3 to 5; prefrail = 1 to 2; robust = 0 • Categories: frail, prefrail, robust
	Chia, et al (2016);¶¶ Tan KY, et al (2017)##	• Weight loss • Grip strength • Exhaustion • Walking speed • Physical activity	• Weight loss: >10 pounds or 5% weight loss in the past year • Grip strength: BMI and gender-specific cutoffs • Exhaustion: "How often in the last week did you feel: (a) everything you did was an effort? (b) you could not get going?" Responses are scored as follows: 1 day = 0; 1 to 2 days = 1; 3 to 4 days = 2; more than 4 days = 3; scoring 2 or 3 on either question is considered exhaustion • Walking speed (15-ft walk): >7 seconds (short: <173 cm males, <159 cm females); >6 s (tall: >173 cm males, >159 cm females) • Physical activity (MLTA): <383 kcal/wk (male); <270 kcal/wk (female) • Cutoff: frail = 3 of the 5 criteria are satisfied • Categories: positive, negative for frailty; frail-positive

AD: Alzheimer's disease; BMI: Body mass index (measured as weight/height); FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; IADL: Instrumental activities of daily living; MCI: Mild cognitive impairment; MFC: Modified Fried Criteria; MLTA: Minnesota Leisure Time Activity; MMSE: Mini Mental State Examination; POMA: Performance Oriented Mobility Assessment

*The Index Reference refers to the original papers cited in the articles.

†Based on a comprehensive geriatric assessment (CGA) where items comprised medical comorbidities, premorbid functional performance in activities of daily living before onset of the acute illness, presence of sensory, and swallowing impairment, laboratory markers, etc.

‡Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85-94.

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Table 4. Conceptual Models of Frailty Identification and Measurement in the Reviewed Articles (Cont'd)

Index Reference*	Reviewed Articles	Frailty Components	Operationalisation, Scoring, and Categories of Frailty
	Vaingankar, et al (2017)***	• Weight loss • Weakness • Exhaustion • Slowness • Low physical activity	• Weight loss: ≥4.5 kg in the last 3 months • Weakness (dominant hand grip strength: lowest 20% by sex, BMI • Exhaustion (self-report): being "worn out or exhausted" • Slowness (5-metre string gait speed): slowest 20% by height and sex • Physical activities (self-report): "not very physically active"; "not at all physically active" • Cutoff: frail, ≥3; prefrail, 1 to 2; non-frail, 0 (no. of parameters) • Categories: frail, prefrail, non-frail
	Wei, et al (2017)†††	• Shrinking • Slowness • Weakness • Exhaustion • Low activity	Modifications to Fried's criteria: • Slowness (gait tests): walked 6 metres back and forth; POMA gait score (0 to 12); <9 denotes slowness • Weakness: lowest quintile of performance based on the POMA • Exhaustion: "Not at all" response to question from SF-12: "Do you have a lot of energy?" • Low activity (physical activity): self-report of "none" for participation in any physical activity • Cutoff: score 1 = for each component present; frail = 3 to 5 points; prefrail = 1 to 2; robust = 0 • Categories: frail, prefrail, robust
Fried (2001)[l]	Chong MS, et al	• Grip strength • Timed walk	• Grip strength (hand dynamometer): <26 kg (males), <18kg (females) • Timed walk (15-ft walk time): <0.8 m/s
Buchman (2007)‡‡‡	Chong MS, et al (2014);§§§ Chong MS, et al (2015)[ll]	• Body composition • Fatigue	• Body composition (BMI): Not specified • Fatigue: Endorsing either item: I felt that everything I did was an effort; I could not get "going" • Cutoff: frail ≥2; non-frail <2 • Categories: frail, non-frail
Morley (2012)¶¶¶	Ng, et al (2014)[#]	FRAIL • Fatigue • Resistance • Ambulation • Illness • Loss of weight	• Fatigue (energy): none of the time • Resistance (aerobic activity): limited a lot • Ambulation (climb stairs): limited a lot • Illness: having ≥5 illnesses • Loss of weight: lost 10 pounds in the past 6 months • Cutoff: score sub-item (0 or 1); frail, ≥3; prefrail, 1 or 2 • Categories: frail, prefrail
	Tan QL, et al (2018)[###]	• FRAIL	Modifications to FRAIL scale: • Frailty was measured using the FRAIL scale questionnaire • Cutoff: score 1 = for each component present; frail = 3 to 5 points; prefrail = 1 to 2; robust = 0 • Categories: frail, prefrail, robust
	Chong E, et al (2018)****	• FRAIL	Modifications to FRAIL scale: • Health state at least 2 weeks prior to any acute illness and/or functional decline or best overall health status over the last 6 months in the absence of acute illness and/or functional decline • Cutoff: frailty ≥3 • Categories: frail, non-frail

AD: Alzheimer's disease; BMI: Body mass index (measured as weight/height); FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; IADL: Instrumental activities of daily living; MCI: Mild cognitive impairment; MFC: Modified Fried Criteria; MLTA: Minnesota Leisure Time Activity; MMSE: Mini Mental State Examination; POMA: Performance Oriented Mobility Assessment

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Index Reference*	Reviewed Articles	Frailty Components	Operationalisation, Scoring, and Categories of Frailty
Physical Frailty – Frailty Index or Index of Deficit Accumulation			
Lunney (2002)††††	Yash Pal, et al (2017)‡‡‡‡	• Chronic frailty	• Patient demographics, comorbidities, premorbid functional status, clinical presentation, previous resuscitation status documentation or discussion, details of death (time, cause of death) from electronic medical records database, which would be available to an emergency physician in clinical practice
Rolfson (2006)§§§§	Tan LF, et al (2018)‖‖‖‖	• Edmonton Frail Scale	• Frailty was measured using the Edmonton Frail Scale and sarcopenia using Sarcopenia-Frailty scale (SARC-F) • Categories: robust, sarcopenic, frail, sarcopenic and frail
Rockwood (2007)¶¶¶¶	Merchant, et al (2016)####	• Function • Strength • Gait characteristics	• Grip strength (<26 kg); 6-minute walk; slow walking speed (<1.0 m/s), and/or • slow time-up-and-go (>10 seconds) • Joint and limb segment: kinematics using 6-camera motion analysis • Cutoff: (Canadian Study for Health and Ageing, CSHA): CFS categories CSHA1 = very fit; CSHA2 = without active disease but less fit than CSHA1; CSHA3 = well, with treated and well controlled comorbidity; CSHA4 = apparently vulnerable, not dependent but complain of being "slowed" and have disease symptoms • Modified CSHA: CSHA1 and 2 = healthy; CSHA3 = intermediate-risk; and CSHA4 = vulnerable • Categories: healthy, intermediate risk, vulnerable
	Chew, et al (2017)****	• CGA†	• 20-item frailty index based on specified criteria in the literature • Cutoff: frailty index ≥0.25 denotes frailty • Categories: frail, non-frail
	Ge, et al (2018)†††††	• CGA†	• Trained nurse assigns the category based on frailty factors (1 to 7) • Clinical Frailty Scale (CFS): F1 (1 to 3), F2 (4), F3 (5), F4 (6 to 7) • Categories: very fit (F1), vulnerable (F2), mildly frail (F3), moderately frail (F4)
Frailty Phenotype versus Frailty Index			
Fried (2001);‖ Hilmer (2009)‡‡‡‡‡	Kua, et al (2016)§§§§§	• Modified Fried Criteria (MFC) • Edmonton Frail Scale	• Slowness (MFC, modified criteria for slowness as hip-fracture patients cannot be tested for gait speed): "positive" if response is positive to any of the questions: "2 weeks ago, were you able to (a) walk up and down stairs to the second floor without help and (b) walk 1 km without help" • Cutoff: ≥3 of the criteria present; MFC, frail = 1 to 5, non-frail = 0 • Categories: frail, non-frail • Edmonton: cognitive impairment, IADL, recent burden of illness, health, depression, weight loss, medication issues, incontinence, inadequate social support, mobility difficulties • Cutoff: severe = 12 to 18; moderate = 10 to 11; mild = 8 to 9; apparent = 6 to 7; non-frail = 0 to 5; frail >7; non-frail ≤7 • Categories: severe frailty, moderate frailty, apparent frailty, non-frail; frail, non-frail
Jones (2004)‖‖‖‖	Chong E, et al (2017);¶¶¶¶ Chong E, et al (2018)#####	• CGA†	• 37-item frailty index based on a comprehensive geriatric assessment • Cutoff: score ≥0.25 (i.e., at least 10 of 37 deficits) • Categories: frail, non-frail

AD: Alzheimer's disease; BMI: Body mass index (measured as weight/height); FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; IADL: Instrumental activities of daily living; MCI: Mild cognitive impairment; MFC: Modified Fried Criteria; MLTA: Minnesota Leisure Time Activity; MMSE: Mini Mental State Examination; POMA: Performance Oriented Mobility Assessment

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Table 4. Conceptual Models of Frailty Identification and Measurement in the Reviewed Articles (Cont'd)

Index Reference*	Reviewed Articles	Frailty Components	Operationalisation, Scoring, and Categories of Frailty
Rockwood (2005)[******]	Chong E, et al (2017);[¶¶¶¶¶] Chong E, et al (2018)[#####]	• CGA†	• 9-point scale: assessor makes a judgement on the degree of frailty • Cutoff: CFS score of 5 to 9 = frail (range 1 to 9) • Categories: frail, non-frail
Gobbens (2010)[††††††]	Chong E, et al (2017);[¶¶¶¶¶] Chong E, et al (2018)[#####]	• Physical • Psychological • Social	• Questionnaire capturing the multidimensional construct of frailty • Tilburg Frailty Index: score ≥5 was diagnostic of frailty (range 0 to 15) • Categories: frail, non-frail
Morley (2012)[¶¶¶]	Chong E, et al (2017); [¶¶¶¶¶] Chong E, et al (2018)[#####]	FRAIL • Fatigue • Resistance • Ambulation • Illness • Loss of Weight	• Health state at least 2 weeks prior to any acute illness and/or functional decline or best overall health status over the last 6 months in the absence of acute illness and/or functional decline • Cutoff: frailty ≥3 parameters • Categories: frail, non-frail
		Combination of Conceptual Models	
Frailty Phenotype + Frailty Index			
Fried (2001);[l] Mitnitski (2002)[‡‡‡‡‡‡]	Lu, et al (2016)[§§§§§§]	• Phenotype: weight loss, weakness, exhaustion, slowness, low physical activity • Index: CGA†	• Phenotype – (a) unintentional weight loss: BMI of <18.5 kg/m² or weight loss of ≥4.5 kg in the past 6 months; (b) dominant knee extension: lowest quintile of a gender- and BMI-adjusted average value from 3 trials; (c) exhaustion: <10/15 on the vitality domain; (d) slowness: <9 in 6-minute fast gait speed test; (e) time (hours) spent daily doing light, moderate and vigorous activities: total time spent per week • Cutoff: score 1 = for each component present; frail = 3 to 5 points; prefrail = 1 to 2; robust = 0 Categories: frail, prefrail, robust • Index – a continuous variable denoting the number of cumulative deficits out of 45 multisystem risk factors • Cutoff: higher value denotes higher risk for frailty (0 to 1)
Physical Frailty + Cognitive Frailty			
Fried (2001);[l] Buchman (2007)[‡‡‡*]	Chong MS, et al (2015);[lllllll] Tay, et al (2016)[¶¶¶¶¶¶]	• Grip strength • Timed walk • Body composition • Fatigue	• Grip strength (hydraulic dynamometer): <26 kg (males), <18 kg (females) • Gait speed (15-ft walk time): <0.8 m/s • Body composition (BMI): Not specified • Fatigue: endorsing either item, "I felt that everything I did was an effort"; "I could not get going" • Cutoff: frail ≥2; non-frail <2 • Categories: frail, non-frail • Also assessed frailty progression/transitions

AD: Alzheimer's disease; BMI: Body mass index (measured as weight/height); FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; IADL: Instrumental activities of daily living; MCI: Mild cognitive impairment; MFC: Modified Fried Criteria; MLTA: Minnesota Leisure Time Activity; MMSE: Mini Mental State Examination; POMA: Performance Oriented Mobility Assessment

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†Based on a comprehensive geriatric assessment (CGA) where items comprised medical comorbidities, premorbid functional performance in activities of daily living before onset of the acute illness, presence of sensory, and swallowing impairment, laboratory markers, etc.

‡Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85-94.

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Fried (2001);[l] Feng (2012)[######]	Feng, et al (2017a);[*******] Feng, et al (2017b);[†††††††] Chye, et al (2018)[‡‡‡‡‡‡‡]	• Shrinking • Slowness • Weakness • Exhaustion • Low activity	Modifications to Fried's criteria: • Slowness (gait tests): walked 6 metres back and forth; POMA gait score (0 to 12); <9 denotes slowness • Weakness (POMA): lowest quintile of performance • Exhaustion (SF-12): responds "Not at all" to "Do you have a lot of energy?" • Physical activity (self-report): participation in physical activity, "none" • Cutoff: score 1 = for each component present; frail = 3 to 5 points; prefrail = 1 to 2; robust = 0 • Categories: frail, prefrail, robust
	Feng, et al (2017a);[†††††††] Chye, et al (2018)[‡‡‡‡‡‡‡]	• Cognitive impairment	• Presence of both physical frailty and cognitive impairment (excluding concurrent dementia) assessed using the MMSE • MMSE: 30 total points, higher score indicates better cognition • Cutoff: Cognitive impairment ≤23; cognitive prefrailty = presence of both physical prefrailty and cognitive impairment, both excluding concurrent dementia or other dementia • Categories: cognitively frail, cognitively prefrail
	Feng, et al (2017b)[†††††††]	• Cognitive impairment	• Modification: mild or greater degrees of cognitive impairment; Chinese MMSE <26 • Categories: no impairment, mild impairment, greater impairment
Morley (2012)[¶¶]	Merchant, et al (2017)[§§§§§§§]	FRAIL • Fatigue • Resistance • Ambulation • Illness • Loss of Weight	Modifications to the FRAIL scale: • Fatigue (energy): none of the time • Resistance (aerobic activity): limited a lot • Ambulation (climb stairs): limited a lot • Illness: having ≥5 illnesses • Loss of weight: lost 10 pounds in the past 6 months • Cutoff: score sub-item (0 or 1); frail = 3 or more; prefrail = 1 or 2 • Categories: frail, prefrail
		• Cognitive impairment	• Modification: cognitive frailty = MMSE score <24 • Categories: cognitively frail, not cognitively frail

AD: Alzheimer's disease; BMI: Body mass index (measured as weight/height); FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; IADL: Instrumental activities of daily living; MCI: Mild cognitive impairment; MFC: Modified Fried Criteria; MLTA: Minnesota Leisure Time Activity; MMSE: Mini Mental State Examination; POMA: Performance Oriented Mobility Assessment

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Index Reference*	Reviewed Articles	Frailty Components	Operationalisation, Scoring, and Categories of Frailty
Physical Frailty + Social Frailty			
Fried (2001);[l] Bunt (2017)[llllllll]	Teo, et al (2017)[¶¶¶¶¶¶¶]	• Shrinking • Slowness • Weakness • Exhaustion • Low activity	• Weight loss: BMI of 18.5 kg/m² and/or unintentional weight loss ≥10 pounds in the last 6 months • Slowness (6-minute fast gait speed test): lowest quintile values stratified for gender and height • Weakness (leg muscle strength using dominant knee extension): lowest quintiles • Exhaustion: "Did you feel worn out/tired/have a lot of energy"; total score <10 (range 3 to 15) • Low activity: average minutes per day spent on physical activities; lowest quintile are classified as low activity • Cutoff: 1 = present, 0 = absent; total score 0 to 5; frail = 3 to 5; prefrail = 1 to 2; robust = 0 • Categories: frail, prefrail, robust
		• Sociodemographic factors	• Living alone: "Who do you live with?" (alone) • No education: "What is your education level?" (Nil) • Absence of a confidant: "Do you have someone to confide in?" (none) • Infrequent contact: none or no more than once a year visits; none or no more than once a year calls from family, friends, or loved ones; none to a very little extent of help when they require it • Infrequent social activities: rarely or do not at all participate in all categories of social activities • Financial difficulties: limited to a great extent to pay for needed medical service • Socioeconomic deprivation: lived in 1-to-2-room flats (housing type) • Cutoff: high = 2 to 7 total; low = 1 total; Nil = 0 • Categories: Social Frailty Index – high, low, Nil

AD: Alzheimer's disease; BMI: Body mass index (measured as weight/height); FRAIL: Fatigue, Resistance, Ambulation, Illnesses & Loss of Weight; IADL: Instrumental activities of daily living; MCI: Mild cognitive impairment; MFC: Modified Fried Criteria; MLTA: Minnesota Leisure Time Activity; MMSE: Mini Mental State Examination; POMA: Performance Oriented Mobility Assessment

*The Index Reference refers to the original papers cited in the articles.

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of sociodemographic indicators where a total score >1 indicates a higher index of social frailty.[22]

Finally, the common physical frailty categories in relevant publications classified older adults into 3 categories: "frail, prefrail, and robust/non-frail". Other papers used dichotomous categories of frailty, such as "frail or non-frail", "frail or prefrail", and "frailty positive or negative".

Discussion

Although the majority of articles in our review examined the physical frailty domain, recent investigations on cognitive and social frailty suggest an important conceptual development in frailty identification research for Singapore. The composite evidence from our review informs immediate next steps in frailty identification research and practice, which primarily relate to streamlining our conceptual understanding of frailty and its measurement as well as addressing the need for implementing optimal measures for its identification.[12] We now discuss the implications of our review findings for research, practice, and policy along with a few insights on important steps moving forward.

Implications for Frailty Research

Our findings on the key conceptual approaches to defining and identifying frailty are consistent with those in the international literature.[6,10] Briefly, the frailty phenotype[7] identifies frailty based on the presence of a set of measurable indicators; whereas the deficit accumulation approach[9] suggests that frailty exists in a spectrum where individuals with more health deficits have a greater risk for adverse outcomes. In 2010, an international study[47] proposed an integral conceptual model of frailty—from which an integral definition of frailty was developed with experts. Their resulting definition identified nutrition, mobility, physical activity, strength, endurance, balance, cognition, sensory functions, mood, coping, social relations and social support as the essential components of frailty. This definition clearly goes beyond the physical domain of frailty—encompassing the cognitive and psychosocial aspects as well.

Notwithstanding the rich knowledge base of frailty identification and the proposed integral definition in previous works, our review of relevant research in Singapore, confirms the lack of consensus on the component elements of frailty and their operationalisation, which has also been reported in previous international studies.[6,10,12] We conjecture that the underlying purpose of measurement[6] and the availability of reliably measured data for analysis[1] can partly explain the observed variations in the component elements examined in eligible articles. Nevertheless, the lack of consistency in frailty components cannot be overstated. Efforts to address the apparent lack of consensus on what constitutes frailty will require a standard frailty definition that specifies a set of component elements and a guide for systematic deviations to the standard definitions, if needed. Standardising the construction of frailty can facilitate the efficient operationalisation of its components as appropriate for research and clinical purposes, which can subsequently allow for greater comparability of measurements across different investigations.

Further research is encouraged to demonstrate the utility of each component element considered in defining frailty.[47] For example, researchers from Duke-NUS Medical School reported that a set of 12 items, which only covers physical frailty variables, has the same ability as a set of 29 items consisting of physical, psychological and social frailty variables to predict a composite of adverse health outcomes among community-dwelling older Singaporeans; after adding age and gender to the 12 physical frailty items, they developed a 14-item Frailty Assessment Measure (FAM).[48] A clear argument from this example weighs into the added benefit of including social and psychological components in the definition of frailty (vs focusing on physical frailty).

Implications for Clinical Practice

The latest AP-CPGMF strongly recommended routine screening for frailty among older adults aged ≥75 years or those individuals with unintentional weight loss.[12] Identifying frailty clearly requires adopting a standard definition and operationalisation of its component elements; however, this assertion raises a related question on the need for a standard measure or scale. Current guidelines recommend using a validated tool for identifying and measuring frailty (vs reliance on crude subjective assessments of visual appearance). The need for selecting the tool that best matches clinical goals is also emphasised.[12]

Conveniently, a pool of validated measurement tools is currently available (Table 4) to provide researchers, clinicians, and/or administrators with a range of measures from which they can select the most appropriate one for their respective purpose. Clinicians are likely to use measures that are easy to integrate in their clinical practice and have demonstrated sound predictive ability to detect functional decline. Whereas administrators, given their intrinsically different purpose for measurement, may consider using other measures based on readily available data from the database of a relevant government agency.[6,10]

Irrespective of the specific goals of measurement, it is essential to select a tool that accurately identifies frailty and predicts relevant patient outcomes. However, beyond testing the psychometric properties of a measurement tool, it is also important to consider its feasibility (i.e., ease of use; fit with the goals of measurement and the resources available). Although most of the available tools have been described as appropriate for clinical settings and have been

regularly used in the region for its predictive value in relation to important health outcomes (e.g., mortality, disability, healthcare utilisation), practical aspects of using these measures largely influence decisions in actual measurements in the clinical setting.[12] Some of the practical considerations include labour and time requirements for administration, training requirements for use, and the need for assessors with highly developed clinical judgement.

Detailed assessment of the outcomes examined in the eligible papers is beyond the scope of our review. Nevertheless, we noted a number of papers that considered the predictive validity of specific frailty measures in detecting adverse health outcomes.[17,19,21,29,30,32,33,46,49] Such papers are especially relevant for clinicians and administrators who are interested in identifying patients at risk for negative outcomes. Measures with low positive predictive value result in an undesirable number of false-positives that may translate to channelling already limited resources into a frailty management plan that will not benefit patients, mainly because they are non-frail to begin with and may have better benefit from prevention programmes. Nevertheless, such measures with high negative predictive values can still be useful in ruling out frailty and reassuring that providers recommend care plans that do not harm an older patient subjected to an unnecessary intervention.[10,50] Awareness of clinically important characteristics of screening tools will not only facilitate the sound interpretation of frailty measures but also better support the implications of measurements for research, policy, and practice.

Lastly, identifying older adult populations who undergo frailty transitions can help in targeting groups who may be more responsive to specific interventions than others in terms of reversing their condition.[25] Despite evidence that certain older adult groups can transition to different frailty states,[25,26] current guidelines[12] mainly focus on screening for individual frailty components (e.g., shrinking, malnutrition, etc.) and the management of older adults who have already been identified to have frailty. Specific recommendations for the management of individuals identified as prefrail may provide further benefits in terms of maximising the opportunity to address reversible frailty states.

Policy Implications

The Singapore Ministry of Health has recognised the lack of agreement in the measures used in systematically identifying frailty and transitions across frailty states. The 2017 National Innovation Challenge (NIC) grant call focused on developing an "appropriate and efficient method" of identifying frailty in older adults to ultimately reduce the risk, delay the onset and/or slow down the progress of physical frailty.[51] The ongoing studies from the NIC initiative will add new insights to relevant discussions on frailty identification and measurement in Singapore. An NIC grant recipient is required to test-bed an evidence-based approach in frailty assessment to ensure the viability of the approach in the community setting and its validity in the local context. This requirement can therefore facilitate a more timely translation of research findings into policy and practice. Stakeholders can then reasonably anticipate new solutions from these projects that can help address the unresolved issues in frailty identification and measurement (e.g., lack consistency in frailty components; need for specific guidelines on selecting appropriate measures).

Reinforcing Frailty Research for Evidence-based Practice and Policy

It is imperative to bring together the foregoing discussion and highlight the importance of reinforcing frailty research for evidence-based practice and policy. Evidence-based guidelines can better target prevention programmes for older adults who are non-frail or prefrail, while focusing on improving management among those identified to have frailty. The latest AP-CPGMF cited the lack of supporting evidence from full systematic reviews in the current recommendations.[12] This scoping review can inform the development of a more rigorous systematic review on the key principles specific to frailty identification and measurement. Furthermore, expert researchers and practitioners in the area of frailty can consider adapting standardised methods for evidence synthesis in the iterative process of guideline development and revision. Achieving a consensus on the definition of frailty and the operationalisation of its components remains a key cog in the wheel that can enable evidence-based practice and policy.

Strengths and Limitations

Our scoping review is the first to summarise the extent of frailty identification research in Singapore. Importantly, this paper engages the local research and medical communities on frailty and related conditions (i.e., sarcopenia). However, we need to consider the findings and implications discussed with a few caveats. Unlike full-scale systematic reviews that aim to present the most comprehensive evidence synthesis in a specific area, the purpose of our review is limited to presenting published research from Singapore in the field of frailty identification in terms of its volume, nature, and characteristics. Although our paper can contribute in informing relevant practice and policy, the relevant implications suggested may be especially limited by the restricted focus on the outcomes investigated and the lack of a standard methodological quality assessment of the papers we included.[13] Moreover, our review is limited to published works in frailty research; this approach essentially excluded available frailty measures that are relevant to clinicians and

researchers, but are still in the publication pipeline (e.g., FAM) as of this writing.

Despite these limitations, the foregoing discourse has substantial contributions to frailty identification and measurement research in Singapore. Presenting the current state of research in the local context uncovers the immediate and long-term needs in this area which future research can address. Given the availability of measurement tools for frailty identification, conducting systematic reviews of measurement properties of available tools in different groups of older adult populations can guide the decision on the optimal measure to be used in specific populations. Such a review will enable the evaluation of the methodological quality of studies that investigate the measurement properties of relevant measurement tools, which can ultimately improve the assessment of synthesised findings. In the same vein, our findings suggest pursuing further primary research on the measurement properties (i.e., validity, reliability, responsiveness) of individual frailty measures, as well as their feasibility and interpretability in specific settings and populations in Singapore. Finally, investigators are encouraged to follow a standard approach in reporting the methodology and findings of their frailty measurement studies to facilitate future evidence synthesis.

Conclusion

In closing, our scoping review provides a broad evidence synthesis of the underpinnings of research on frailty identification and measurement in Singapore. Presenting the available evidence is an essential first step in engaging the local community of researchers and clinicians to move towards improving consistency in frailty measurement. Together, researchers, clinicians, and administrators can enable effective and timely evidence-based practice and policies that can ultimately benefit older adults in Singapore.

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Appendix 1 – Search Strategy

Concept	Key Words	PubMed MeSH	CINAHL Subject Terms	Equivalent Terms
#1 Frailty	frailty or frail or vulnerable or vulnerability	"Frailty"[Mesh]	(MH "Frailty Syndrome")	frail or frailty or vulnerable or vulnerability
		"Frail Elderly"[Mesh]	(MH "Frail Elderly")	"frail elderly"
And				
#2 Older Adults	aged or elderly	"Aged"[Mesh]	(MH "Aged")	aging or ageing or "older adult" or "older adults"
And				
#3 Identification (definition, markers)	risk factors	"Risk Factors"[Mesh]	(MH "Risk Factors")	"risk factor" or "risk factors"
	association	"Association" [Mesh]	None	associated or association
	health status indicators	"Health Status Indicators"[Mesh]	(MH "Health Status Indicators")	"health status indicators"
	markers or biological markers or clinical markers	"Biomarkers"[Mesh] or "Genetic Markers"[Mesh]	(MH "Biological Markers") or (MH "Genetic Markers")	markers or "biological markers" or "clinical markers"
	gait speed	"Walking Speed"[Mesh]	(MH "Gait")	"gait speed" or "walking speed" or "walking pace"
	physical activity	"Exercise"[Mesh]	(MH "Physical Activity")	"physical activity"
	weight loss	"Weight Loss"[Mesh]	(MH "Weight Loss")	"weight loss"
	cognitive impairment	"Cognitive Dysfunction"[Mesh]	None	"cognitive impairment" or "cognitively impaired"
	depressive symptoms	"Depression"[Mesh]	(MH "Depression")	"depressive symptoms" or depression
	exhaustion	None	None	exhaustion
	weakness	None	None	weakness
	hand grip strength	"Hand Strength"[Mesh]	(MH "Grip Strength")	"grip strength"
	deficit or accumulation or cumulative	None	None	deficit or accumulation or cumulative
	identification, assessment, measurement	None	None	identification or identifying or identified or measurement or measuring
And / Or				
#4 Identification (Methods)	health surveys	"Health Surveys"[Mesh]	(MH "Surveys")	questionnaire or questionnaires or survey
	diagnosis	"Diagnosis"[Mesh]	(MH "Diagnosis")	diagnosis
	rating scales or index	None	None	"rating scales" or index
	risk assessment or case finding or geriatric assessment	"Risk Assessment"[Mesh] or "Geriatric Assessment"[Mesh]	(MH "Risk Assessment") or (MH "Geriatric Assessment")	"risk assessment" or "case finding" or "geriatric assessment"
	disability evaluation	"Disability Evaluation"[Mesh]	(MH "Disability Evaluation")	"disability evaluation"
	forecasting	"Forecasting"[Mesh]	(MH "Forecasting")	forecasting
	patient care planning	"Patient Care Planning"[Mesh]	(MH "Patient Care Plan")	"patient care plan" or "patient care planning"
And				
#5 Singapore	Singapore	"Singapore"[Mesh]	(MH "Singapore")	Singapore
			PubMed: (#1 and #2) AND (#3 or #4) and #5	137 records
			CINAHL: (#1 and #2) and (#3 or #4) and #5	28 records
			Combine PubMed2 + CINAHL2	**165 records with 23 duplicates**
			Unique records in PubMed + CINAHL for Title and Abstract Screening	**142 records for title and abstract screening**

Notes: No additional limits/search filters were applied; Last date of search: 8 May 2018 (PubMed and CINAHL); Articles that are not indexed in PubMed on the last date of search are not included in the search results. Key references used in developing the search strategy: Elliott, A., L. Hull, and S.P. Conroy. Age Ageing, 2017. 46(3): p. 509-513; Lee, L., et al. Geriatr Gerontol Int, 2017. 17(10): p. 1358-1377; Drubbel, I., et al. BMC Geriatr, 2014. 14: p. 27; Sternberg, S.A., et al., *The identification of frailty: a systematic literature review.* J Am Geriatr Soc, 2011. 59(11): p. 2129-38

Relapsing Course of Sulfasalazine-Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Complicated by Alopecia Universalis and Vitiligo

Dear Editor,

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a drug-related severe cutaneous adverse reaction characterised by a delayed latency, multi-organ involvement, reactivation of human herpes virus as well as a chronic relapsing course. Various autoimmune associations following the development of DRESS have been described—including autoimmune thyroid disease and type 1 diabetes.[1,2] The exact pathogenesis of autoimmunity remains unclear although a delayed dysfunction of T reg cells and association with viral reactivation have been postulated.[2-5] We present a case of sulfasalazine-induced DRESS that is complicated by a relapsing course and concurrent vitiligo and alopecia universalis.

Case Report

The patient is a 59-year-old male with a history of rheumatoid factor-positive erosive rheumatoid arthritis, initially treated with methotrexate for a duration of 10 months and subsequently switched to sulfasalazine. Two months after starting sulfasalazine of progressively increasing doses (1 g daily for 1 week, then 1.5 g daily for 1 week, then 2 g daily for 6 weeks), he developed a generalised, pruritic scaly dermatosis characterised by facial oedema and swelling with confluent erythema affecting 70% of his body. Over the course of the next 2 months, he developed fever, absolute eosinophil count of 2.99 × 10^9/L (upper limit of normal: 0.04 x 10^9/L), renal impairment: creatinine 127 µmol/L (reference: 37-75 µmol/L), mild hepatic impairment: alanine aminotransferase 78 IU/L (reference: 6-66 IU/L), aspartate aminotransferase 29 IU/L (reference: 12-42 IU/L) and cytomegalovirus (CMV) reactivation. Skin biopsy performed showed mild spongiosis with neutrophil extension into the superficial epidermis; the papillary dermis was oedematous with proliferated capillaries and a diffuse interstitial as well as perivascular polymorphous inflammatory cell infiltrate. A diagnosis of DRESS was made. The calculated RegiSCAR diagnostic score[6] was 6 (based on: eosinophilia, skin rash >50%, oedema and scaling, 1 internal organ involved, 3 biological investigations done and negative to exclude alternative diagnosis). He was initially treated with systemic corticosteroids (prednisolone: 40 mg daily, 0.5 mg/kg) which was gradually tapered, with cyclosporine (highest dose of 225 mg daily, 3 mg/kg) being added 2 months later.

However, he continued to have intermittent flares characterised by erythematous scaly plaques which was associated with CMV reactivation based on polymerase chain reaction (PCR). CMV titres were noted to decrease with improvement in the skin. Six months after the onset of the rash, he developed diffuse non-scarring alopecia affecting his scalp, axilla, genitals and eyebrows consistent with alopecia universalis (Fig. 1); as well as depigmented macules over his lower back and abdomen consistent with vitiligo (Fig. 2). At that time, his treatment consisted of prednisolone 12.5 mg daily and cyclosporine 100 mg daily. Thyroid function and glucose levels done prior were normal. Although this improved his cutaneous flares, the alopecia and vitiligo remained. He had no further recurrences of DRESS although the depigmentation and hair loss remained permanent. Both prednisolone and cyclosporine were stopped 19 months after onset of the rash.

Discussion

DRESS is a drug-related severe cutaneous adverse reaction characterised by a variable cutaneous eruption with blood eosinophilia and visceral organ involvement.[6] Patients with DRESS are often treated with the use of systemic corticosteroids.[7] Clinical improvements with the use of corticosteroids are believed to suppress excessive immune responses to drug metabolites and/or inhibit the

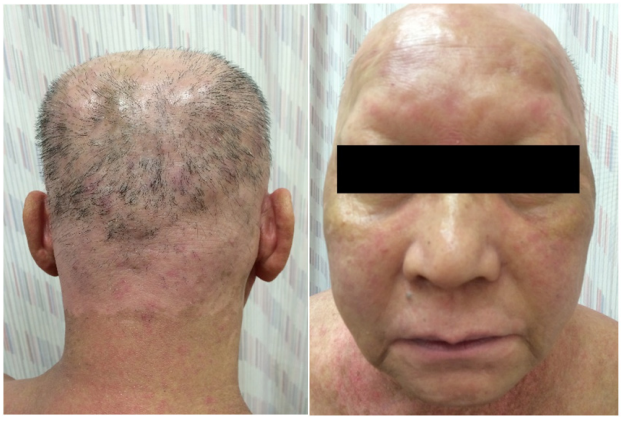

Fig. 1. Development of alopecia universalis with gradual loss of scalp hair and eyebrows at 3 and 5 months from onset of rash.

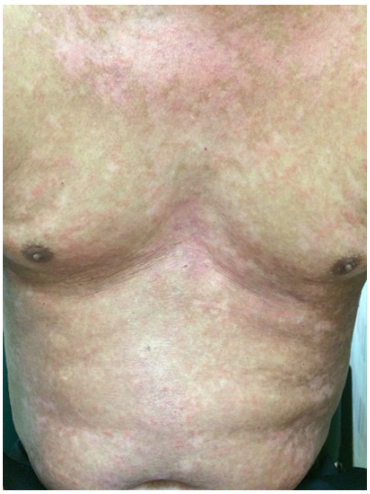

Fig. 2. Presence of vitiligo over the chest and abdomen at 6 months from onset of rash.

production of cytokines caused by massive replication of viruses.[8] However, the use of corticosteroids and concomitant immunosuppression give rise to an increased risk of infectious complications.[9] CMV reactivation after the onset of DRESS has been previously reported[3] and was seen in our patient. This discordance between controlling the immune response and viral reactivation in DRESS makes therapy difficult and a careful balance must be struck while adjusting the corticosteroids.

DRESS has also been associated with the development of long-term autoimmune sequalae such as Graves' disease, Hashimoto's thyroiditis, type 1 diabetes mellitus and autoimmune haemolytic anaemia.[3,4] Reports regarding autoimmune dermatological sequalae following DRESS are limited. Our patient developed a combination of alopecia universalis and vitiligo. The underlying pathophysiology for the development of autoimmune sequalae are unclear at present. Studies done have posited viral infection or reactivation and the subsequent dysfunction of regulatory T cells as possible mechanisms underlying such sequalae.[3,5]

In view of sequalae of viral reactivation and autoimmune complications after onset of DRESS, the monitoring of patients even after resolution of the cutaneous eruption is essential.

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Percutaneous Radiologically-Guided Gastrostomy (PRG): Safety, Efficacy and Trends in a Single Institution

Dear Editor,

Percutaneous radiologically-guided gastrostomy (PRG) was first described in animal studies in 1983,[1] shortly after the first publication of percutaneous endoscopic gastrostomy (PEG) in human subjects in 1980.[2] Since then, PEG has been more widely adopted and considered the preferred standard of care.[3] Despite this difference in popularity, a recent meta-analysis[4] failed to show superiority of one technique over the other in terms of safety and efficacy.

Gastrostomy catheter insertion is usually indicated for long-term enteral nutrition in patients with difficulty maintaining adequate nutrition orally.[3] This includes patients with obstructive lesions of the upper aerodigestive tract or neurological conditions that impair swallowing.

PEG requires per-oral insertion of a flexible endoscope into the stomach, with transillumination through the upper abdominal wall to guide percutaneous placement of the gastrostomy catheter.[3] In contrast, PRG does not require endoscopy, instead relying on sonographic or fluoroscopic guidance. In our centre, all PRGs were inserted via the retrograde abdominal approach where T fasteners are inserted under fluoroscopic guidance into an inflated stomach before introducing the gastrostomy tube retrogradely[4] (Fig. 1). We perform the PRG under local anaesthesia only or with moderate to deep sedation.

Proponents of PRG state a higher technical success rate over PEG,[5,6] no absolute contraindication[7] and less procedural sedation required.[6-8] However, several studies have concluded that PRG results in a higher complication rate and mortality in comparison to PEG.[9-12] This study aimed to examine the safety and efficacy of PRG insertion performed in our centre.

Materials and Methods

We performed a retrospective review of 85 patients receiving PRG in our centre between February 2003 and February 2017. Study approval was obtained from our institutional review board. Our centre offers both PEG and PRG services, with patients cared for under a multidisciplinary team approach. Patients were referred for PRG insertion based on the discretion of the referring clinician, as well as when PEG was contraindicated. Medical records and procedural images were reviewed, and the data assessed for primary outcomes of procedure success, mortality related to the procedure and mortality within 30 days from any cause.

Complications occurring within 30 days and related to the procedure were also measured and further subdivided into major and minor complications. We followed the Common Terminology Criteria for Adverse Events (CTCAE), v4.0,[13] created by the United States' Department of Health and Human Services. Major complications (CTCAE grade 4) were defined as life threatening and requiring immediate and aggressive intervention, including but not limited to, severe persistent haemorrhage, peritonitis, bowel perforation, and pulmonary, cardiac and neurological events. Minor complications (CTCAE grades 1-3) were defined as not life threatening and requiring little or no intervention, such as tube dislodgement, tube blockage or superficial cellulitis.

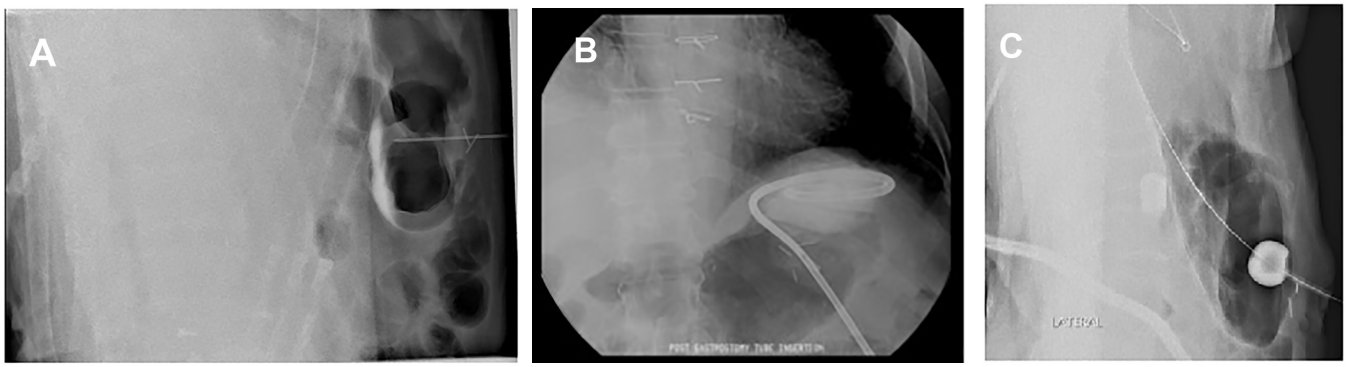

Fig. 1. A: Lateral view showing the T fasteners opposing the anterior gastric wall to the abdominal wall, which were inserted via earlier similar punctures after gastric distention. Final needle puncture before gastrostomy insertion. Note the contrast in the stomach, which was injected after each puncture for confirmation. B: Postcatheter insertion of loop gastrostomy tube. C: Postcatheter insertion of balloon gastrostomy tube.

Results

Patients recruited were 76.5% male with a mean age of 63.9 years (Table 1). The most common indication for PRG (Table 1) was oro-pharyngeal obstruction due to nasopharyngeal tumour (35.3%). Neurological indications such as cerebrovascular accident and motor neuron disease only accounted for 12.9% of PRG insertions. Various malignancies obstructing the upper aerodigestive tract such as laryngeal and oesophageal tumours accounted for all remaining insertions.

Table 1. Patient Characteristics Including Demographic Data, Procedure-Related Statistics and Indications for Procedure

Patient Characteristics	**n**	**(%)**
General		
Age (years, mean [SD])	63.9	(14.3)
Sex		
Male	65	(76.0)
Female	20	(24.0)
Prior NG feeding (n = 55, 64.7%)		
>30 days duration	34	(61.8)
Procedure-Related	**n**	**(%)**
Technical success	85	(100.0)
Type of G tube (balloon)		
Balloon catheter*	69	(81.2)
Non-balloon catheter†	16	(18.8)
Number of gastropexy tags		
2 tags	57	(67.1)
3 tags	28	(32.9)
Type of anaesthesia (n = 78)		
LA only	47	(60.3)
LA + sedation	31	(39.7)
Indications	**n**	**(%)**
Malignancy		
Nasopharyngeal tumour	30	(35.3)
Oropharyngeal tumour	5	(5.9)
Laryngeal tumour	14	(16.5)
Oesophageal tumour	13	(15.3)
Gastric tumour	1	(1.2)
Sinonasal tumour	3	(3.5)
Salivary gland tumour	2	(2.4)
Thyroid tumour	1	(1.2)
Lung tumour	4	(4.7)
Neurology		
Dementia	2	(2.4)
Motor neuron disease	3	(3.5)
Parkinson disease	3	(1.2)
Stroke	1	(1.2)
Olivopontocerebellar atrophy	1	(1.2)
Glioblastoma multiforme	1	(1.2)
Miscellaneous		
Boerhaave syndrome	1	(1.2)

G: Gastrostomy; LA: Local anaesthesia; NG: Nasogastric; SD: Standard deviation
*Balloon catheters used were 16-18F.
†Non-balloon catheters used were 14F.

Prior to PRG insertion, 55 patients (64.7%) were already on naso-enteric tube feeding (Table 1). Thirty four of these 55 patients received naso-enteric feeds for more than 30 days, with a median time of 57 days (range 5-1628 days) continuously receiving naso-enteric nutrition.

A 100% technical success rate was achieved with zero procedure-related mortality, and 30-day all-cause mortality at 10.9% (Table 2). Only 3 major complications (3.5%) occurred (described below), minor complications were relatively low as well, with an infection rate of 8.2%, tube dislodgement rate of 7.1% and tube occlusion rate of 3.5%.

In 1 patient with a non-inflated stomach due to Boerhaave syndrome, computed tomography (CT) guidance was successfully utilised for imaging guidance after a failed endoscopic nasogastric (NG) tube insertion. An initial puncture was performed using the AccuStick introducer system (Boston Scientific, Marlborough, MA, United States) under ultrasound guidance allowing partial inflation of the stomach. Two anchors were then placed under CT guidance, with the catheter then inserted between the anchors over a guide wire (Fig. 2). The patient was successfully fed for 1 month through the gastrojejunostomy tube before terminal discharge. The decision for conservative management was made in view of the high risk involved in surgical intervention and the patient's advanced age and multiple comorbidities.

One patient suffered from severe bleeding which occurred as a result of injury to the left gastroepiploic artery during the procedure and required exploratory laparotomy with

Table 2. Complications and Mortality Postprocedure

Complications	**n**	**(%)**
Major		
Severe bleeding*	1	(1.2)
Persistent pneumoperitoneum†	1	(1.2)
Gastric fundus perforation	1	(1.2)
Minor		
Infection	7	(8.2)
Tube dislodgement	6	(7.1)
Tube occlusion	3	(3.5)
Mortality	**n**	**(%)**
30-days mortality	9	(10.6)
Procedure-related mortality	0	(0.0)

*Severe bleed requiring laparotomy due to inadvertent ligation of aberrant right gastroepiploic artery.
†Persistent pneumoperitonium resulting in peritonitis.

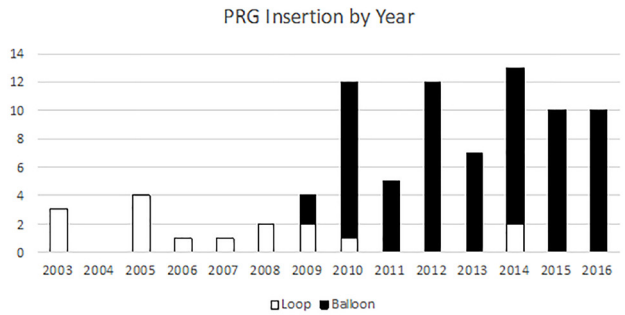

Fig. 2. Graph showing the number of percutaneous radiologically-guided gastrostomy (PRG) per year, further separated by type of gastrostomy tube (loop or balloon). Increasing trend of gastrostomy adoption is seen, as well as gradual transition from loop to balloon catheter over the years.

surgical haemostasis. Another 80-year-old patient had persistent pneumoperitoneum postprocedure, also requiring laparotomy, where it was found that there was poor anchoring of the stomach to the anterior abdominal wall with no evidence of the expected inflammatory reaction and healing around the catheter track. The catheter was therefore removed and omental patch repair performed, and the patient made an uneventful recovery with return to full NG feeding. A case of gastric fundus perforation was discovered during the procedure, and was likely caused by the guide wire. The small perforation was successfully clipped during endoscopy on the same day.

Discussion

Our results show PRG to be highly effective with a low complication rate and procedure-related mortality. This is largely in keeping with current literature.[5-7,12,14,15] A 2016 Cochrane analysis[4] documented a range of major complication rate of 1.4% to 5.6%, which is in line with our own study finding of 3.5%. High technical success rate is also seen in other studies,[6,9,16] with authors reporting similar success rates of 99% to 100%.

The most common indication for PEG has historically been cerebrovascular accident,[3,5] including within our own centre.[17] In contrast, nasopharyngeal tumours was the commonest indication for PRG in our study. This reflects the usefulness of PRG in patients who may be considered more difficult PEG candidates due to oral or upper gastrointestinal tract obstruction,[15] where passage of a flexible endoscope per-orally may be technically challenging.

Several other indications favoured PRG over PEG. These include—but are not limited to—poor transillumination of the abdominal wall in patients with obesity or high subcostal stomach[14] and rare cases of tumour seeding at the PEG exit site for patients with head and neck cancer.[9] In patients with altered anatomy, PRG may also be preferred, as preprocedural radiological planning would allow for modified approaches where appropriate. This is well illustrated by our patient with Boerhaave syndrome.

The rising trend of adoption of PRG in our centre is likely due to increased physician and patient awareness and outreach by interventional radiologists. The increased usage of balloon catheters (Fig. 3) is likely due to the interventional radiologists' preference and the trend worldwide to use these devices.

PRG, however, remains a secondline intervention before PEG in many centres.[3,5] One meta-analysis of 15 peer reviewed studies comparing PEG and PRG[18] demonstrated similar 30-day mortality of 10.5% (95% CI, 6.8%-14.3%) for PRG insertion compared to our own study's 30-day mortality of 10.6%. In comparison, PEG insertion was found to have statistically significantly lower 30-day mortality of 5.5% (95% CI, 4.0%-6.9%). However, retrospective study designs and lack of randomisation prevented conclusive recommendations advocating for one method over the other in this and other analyses.[5,12] It is also our view that this apparently higher mortality amongst patients receiving PRG insertion may be a result of patient selection rather than factors intrinsic to the procedure itself. Patients referred for PRG insertion in our centre tend to be generally more ill and unfit for procedural sedation. Further prospective studies may be required to definitively answer this important clinical question.

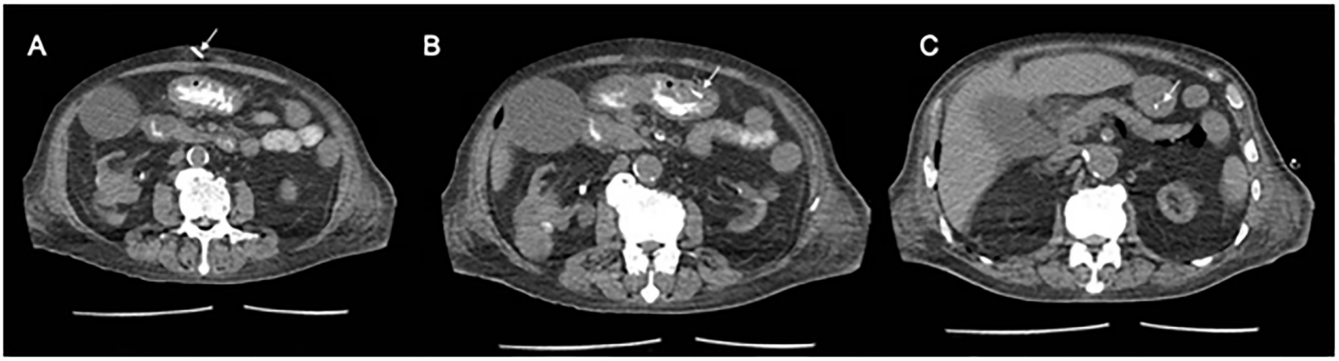

Fig. 3. Selected intraprocedural computed tomography (CT) of percutaneous radiologically-guided gastrostomy (PRG) insertion for a patient with Boerhaave syndrome, showing the course of the wire (white arrow). A: Through the skin and subcutaneous tissue. B: Through the non-distended stomach wall. C: In the lumen of the gastric fundus. The stomach was then inflated via a catheter which was threaded over this wire to resume the usual steps of PRG insertion.

The majority of our patients were on continuous NG feeding for longer than 30 days prior to PRG insertion, exceeding the recommendation for duration of naso-enteric feeding before conversion to gastrostomy.[3] This likely reflects late physician referral for conversion to gastrostomy. Physicians anticipating patients in need of long-term enteral nutrition should seek early referral for gastrostomy tube insertion within 2 to 3 weeks of continuous NG feeding rather than leaving gastrostomy as an option of "last resort". The benefits of gastrostomy over long-term NG feeding include lower rate of aspiration and extubation in elderly patients[19] as well as improved nutrition with slower initial weight loss in patients with head and neck cancers.[20] In addition, patients who are already malnourished from disease and feeding difficulties naturally will benefit less from any procedure and have higher procedural-related risks.

As shown in the earlier example, CT fluoroscopy and ultrasound have allowed the puncture of the non-distended stomach in conditions where a NG tube insertion is not possible. These conditions include complete upper digestive tract obstruction,[21] patients with failed endoscopy[22] as well as following Roux-en-Y gastric bypass surgery.[23]

One other recent advancement has seen the transition to a 1-step direct low-profile catheter insertion. Previously, the standard balloon tube was first inserted to allow the catheter track to mature, before a percutaneous tube change to a low-profile catheter was performed at a later stage. Low-profile catheters are flushed to the skin, and as such last longer than standard balloon tubes due to a lower risk of dislodgement,[24] while also providing greater comfort and more acceptable appearance to the patient.[25]

This study has several limitations. As a retrospective study, patients were selected based on physician referral and differences in technique depended on the interventional radiologist performing the procedure. While we found no statistically significant differences in outcomes when comparing procedural techniques employed, such as use of balloon or loop catheter, number of gastropexy tags applied or use of procedural sedation, this could be due to the small sample size. Further analysis with a larger sample size across several centres would provide further insight into how differences in procedural technique may account for differences in outcome.

Conclusion

In conclusion, PRG should be considered as a useful alternative to PEG. The results of this study demonstrated 100% technical success, zero procedure-related mortality and a low complication rate. The inability to insufflate the stomach is no longer an absolute contraindication to PRG. We recommend that physicians make earlier referrals for patients with a projected course of enteral nutrition which may exceed 30 days rather than to wait until later stages of their disease, so they can benefit from gastrostomy feeding early. As with most other care models, a multidisciplinary approach is the key to select the best enteral feeding methods for different groups of patients. Thus, members within this team should be aware of the strengths and weaknesses of each technique.

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