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ORIGINAL RESEARCH

Sepsis in a Combined Medical and Surgical High Dependency/Intensive Care Unit in Singapore: A Cohort Study and Survival Analysis

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Background: Sepsis is a common indication for intensive care unit (ICU) admission and is associated with significant mortality and morbidity. The aim of our study was to first assess the incidence, severity, short-term and long-term mortality of sepsis in a combined medical and surgical high dependency/ ICU in Singapore, and to identify factors associated with increasing short-term and long-term mortality.

Methods: All admissions from July 1 to December 31, 2017 were retrospectively screened and clinical data were collected. Patients were followed up until 3 years post ICU admission.

Results: Of a total 1526 admissions, 281 had infection at ICU admission, and 254 (16.6%) fulfilled sepsis-3 criteria for sepsis. A total of 141 (9.2%) had septic shock. The 30-day, 1-year, 2-year and 3-year mortality of sepsis patients were 19.3%, 25.2%, 30.3% and 32.3%, respectively. Lung was the most common site of infection. Compared with 30-day sepsis survivors, non-survivors were older (median age 70 vs 63, P <0.001), had higher percentage of lung infection (65.3% vs 36.1%, P <0.05), higher admission Sequential Organ Failure Assessment (SOFA) score (median 9 vs 5, P <0.001), and longer ICU stay (median days: 4 vs 3, P = 0.037). In stepwise Cox regression analysis, lung infection was an independent risk factor for both increasing 30-day and 3-year mortality. Immunocompromised host, increasing age and SOFA score were associated with higher 30-day mortality. Diabetes, admission quick Sequential Organ Failure Assessment (qSOFA) score >1 and unplanned ICU re-admission were associated with increasing 3-year mortality in 30-day survivors.

Conclusion: Our retrospective cohort single center study first reported sepsis admission incidence of 16.6% in a combined medical and surgical high dependency/ICU in Singapore, with significant short-term and long-term mortality. Lung infection was an independent risk factor for both 30-day and 3-year mortality.

Keywords: sepsis, septic shock, incidence, severity, mortality, intensive care unit

Introduction

Sepsis, defined as a dysregulated host response to infection,[1] causes significant mortality and morbidity in the intensive care unit (ICU), with significant negative economic impact.[2] Incidence of ICU sepsis was reported between 1.6–290 per 100,000 person-years.[3] It varied geographically, ethnically and in different types of ICUs. In a multicenter prospective cohort study of Asian ICUs (MOSAICS study), incidence of sepsis ranged from lowest of 5.5% (India) to highest 53.9% (Nepal). Hospital mortality was as high as 44.5%, and was related to country income status, hospital and ICU structure.[4]

Though many epidemiology studies have been done on ICU sepsis, detailed reports of its severity and long-term mortality are few. As the first combined medical and surgical integrated High Dependency Unit/ICU in Singapore facing a complex high acuity case mix, for quality improvement purposes, we conducted this retrospective cohort study to first assess the incidence, severity, short-term and long-term mortality of sepsis in our unit population under the new ICU structure.

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Method

Study Population and Design

Our unit was the first integrated multi-disciplinary High Dependency and ICU in Singapore serving a joint 1000-bed acute and community hospital, with 2500–3000 admissions annually including medical (45%), trauma/ surgical (30%) and cardiac (25%). It features 74 critical care single rooms (currently operating 34 beds) that can be easily converted between ICU (requirement of Invasive mechanical ventilation or at least 2 organ system support, 1:1 patient-to-nurse ratio) and High Dependency (requirement of non-invasive ventilation or single organ support, 2:1–3:1 patient-to-nurse ratio) status. It is an accredited training unit of the Singapore Medical Council and College of Intensive Care Medicine of Australia and New Zealand.

Electronic medical record of all admissions to the unit from July 1 to December 31, 2017 were reviewed. Data collected were demographic characteristics, comorbidities, admission vital signs, clinical sites of infection, microbiology results, length of stay, event of unplanned ICU re-admission within the same hospitalization. Death at 30-day, 1-year, 2-year, 3-year after ICU admission was recorded. A study algorithm is shown in Figure 1.

Study Ethics

Our study was approved by National Healthcare Group Domain Specific Review Board with exemption (reference number 2019/00247) and conducted in accordance with the Declaration of Helsinki. Informed consent was waived as it was retrospective extraction of existing medical data. Data were processed and analyzed without patients' identifiers.

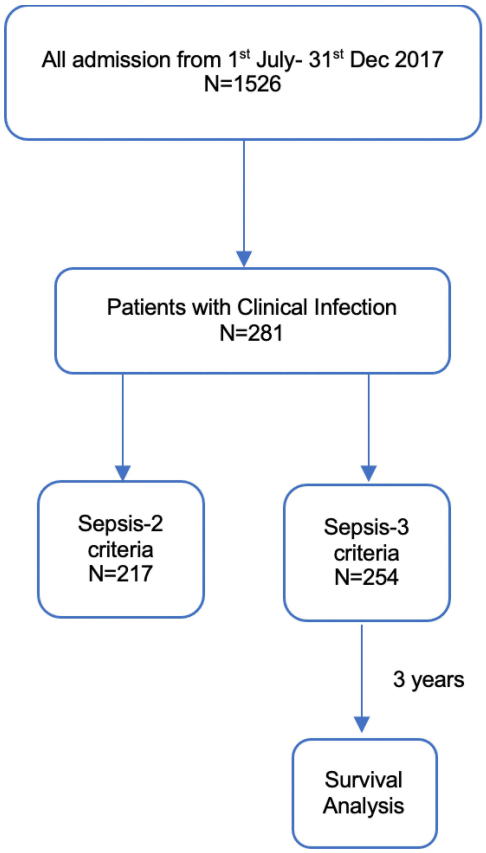

Figure 1 Study algorithm.

Definition

Sepsis was defined as per sepsis-3 criteria as clinical suspicion of infection with a Sequential Organ Failure Assessment (SOFA) score ≥2. Septic shock was defined as clinical context of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mmHg and serum lactate level >2 mmol/L (18 mg/dL).[1] Clinical infection definition followed the consensus by Calandra et al.[5]

Quick SOFA (qSOFA) score was calculated according to the following three parameters: systolic blood pressure ≤100 mmHg, respiratory rate ≥22 breaths/min, and Glasgow Coma Scale (GCS) <15.[1]

In addition to sepsis-3 criteria, patients fulfilling sepsis−2 criteria were also identified to compare pick-up rate of the two definitions. Sepsis-2 criteria defined sepsis as meeting two or more systemic inflammatory response syndrome (SIRS) criteria (Body temperature >38°C or <36°C; Heart rate >90/min; Respiratory rate >20/min or $PaCO_2$ <32 mmHg; Leukocyte count >12,000/mL or <4000/mL or >10% immature neutrophil) in addition to known or suspected infection.[6]

Immunocompromised host was defined as patients with primary or secondary immunodeficiency disorder or from the use of agents that depress one or more components of the immune system.[7]

Data Analysis

Continuous variables were presented as median (minimum-maximum) for non-normal distribution data, and were compared with Mann–Whitney*U* -test. Categorical variables were presented as actual number (percentage) and compared using Chi-square test. Backward stepwise multivariate Cox regression with removal criteria of P >0.15 was used to analyse associating factors with 30-day mortality in all sepsis patients and 3-year mortality in 30-day survivors. Results were presented as Hazard Ratio (HR) with 95% Confidence Interval (CI). A 3-year survival plot with comparison between septic shock group and sepsis without shock group was generated with Kaplan-Meier curve. P <0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences software version 26.0 (International Business Machines Corporation, Armonk, New York, USA).

Results

Incidence and Mortality of Sepsis

There was a total of 1526 admissions to ICU from July 1 to December 31, 2017. Of these 281 (18.4%) had clinical infection, 217 (14.2%) fulfilled sepsis-2 criteria for sepsis and 254 (16.6%) fulfilled sepsis-3 criteria with median SOFA score of 6. Compared with sepsis-2 criteria, sepsis-3 had a higher pick-up rate for sepsis (16.6% vs 14.2%). The 254 patients with sepsis as per sepsis-3 criteria were included in subsequent analysis for severity and mortality. Sepsis patients had median age of 64 years, 60.6% were male and 57% were Chinese. Hypertension (58%) and diabetes mellitus (41%) were common co-morbidities at admission (Table 1). Lung was the most common site of infection (42%), followed by urinary tract (27%) and soft tissue (11%). Eighty-three (32.6%) septic admissions had quick SOFA score (qSOFA) more than 1, 89 (35%) received invasive mechanical ventilation and 88 (34.6%) had positive blood cultures. Median length of ICU stay was 3 days, and 19 (7.5%) admissions had care limitation or withdrawal. Seventeen (6.7%) had unplanned ICU re-admission after discharge to general ward. The 30-day, 1-year, 2-year and 3-year mortality of sepsis patients was 19.3%, 25.2%, 30.3% and 32.3% respectively (Table 2).

Septic Shock vs Sepsis without Shock

Among 254 admissions with sepsis, 141 (55.5%) had septic shock. Compared with patients without shock, the shock group patients were older (median age 66 vs 63, P <0.001), had higher SOFA score at ICU admission (median 9 vs 4, P <0.001), higher percentage with qSOFA >1 (39.7% vs 23.9%, P = 0.01), higher invasive mechanical ventilation rate (52.5% vs 13.3%, P <0.001), and longer ICU length of stay (median days 3 vs 2, P <0.001). However, the non-shock group had higher percentage of chronic lung disease history (27.4% vs 10.6%, P <0.001) and higher incidence of lung infection (51.3% vs 34%, P <0.05) (Tables 1 and 2).

The 30-day mortality (28.4% vs 8%, P <0.001), 1-year mortality (34.8% vs 13.3%, P <0.001), 2-year mortality (39.7% vs 18.6%, P <0.001), and 3-year mortality (41.8% vs 20.4%, P <0.001) were all significantly higher in the septic

Table 1 Demographic Data of Sepsis Patients with Group Comparison

	Total N = 254	Septic Shock N = 141	Sepsis without Shock N = 113	P value	30-Day Survivor N = 205	30-Day Non-survivor N = 49	P value
[a]Age	64 (16–90)	66 (16–90)	63 (25–87)	<0.001	63 (22–90)	70 (16–90)	<0.001
Male (%)	154 (60.6%)	90 (63.8%)	64 (56.6%)	0.248	124 (60.5%)	30 (61.2%)	0.53
Race							
Chinese	145 (57%)	79 (56%)	66 (58.4%)	P>0.05	117 (57.1%)	28 (57.1%)	P>0.05
Malay	51 (20%)	31 (22%)	20 (17.7%)		39 (19%)	12 (24.5%)	
Indian	26 (10%)	14 (9.9%)	12 (10.6%)		22 (10.7%)	4 (8.2%)	
Others	32 (13%)	17 (12.1%)	15 (13.3%)		27 (13.2%)	5 (10.2%)	
Past medical history							
Ischemic heart disease	59 (23%)	37 (26.6%)	22 (19.6%)	0.232	44 (21.7%)	15 (31.3%)	0.113
Cirrhosis	7 (3%)	3 (2.1%)	4 (3.5%)	0.703	6 (2.9%)	1 (2.0%)	0.595
Dialysis	28 (11%)	18 (12.8%)	10 (8.8%)	0.421	20 (9.8%)	8 (16.3%)	0.144
Diabetes Mellitus	105 (41%)	58 (41.1%)	47 (41.6%)	0.521	82 (40%)	23 (46.9%)	0.234
Hypertension	147 (58%)	88 (62.4%)	59 (52.2%)	0.125	113 (55.1%)	34 (69.4%)	0.048
Chronic Lung disease	46 (18%)	15 (10.6%)	31 (27.4%)	<0.001	39 (19%)	7 (14.3%)	0.292
Immunocompromised host	9 (4%)	5 (3.6%)	4 (3.5%)	0.631	6 (2.9%)	3 (6.3%)	0.232

Note: [a]Presented as median (Min-Max).

shock group (Table 2). The 3-year survival plot showed a significant difference between septic shock and non-shock group (P <0.001) (Figure 2). Sex and race distribution, care limitation and unplanned ICU re-admission rate were similar between the two groups (Tables 1 and 2).

Survival Analysis

Compared with 30-day sepsis survivors, non-survivors had older age (median age 70 vs 63, P <0.001), higher rate of lung infection (65.3% vs 36.1%, P <0.05), higher SOFA score at ICU admission (median 9 vs 5, P <0.001), and longer ICU stay (median length of stay days 4 vs 3, P = 0.037) (Tables 1 and 2). In stepwise Cox regression analysis, increasing age (HR= 1.028, 95% CI [1.005–1.051], P = 0.01), immunocompromised host (HR = 5.254 [1.495–28.464], P = 0.01), lung infection (HR = 4.802 [2.567–8.982], P <0.001) and increasing ICU admission SOFA score (HR = 1.206 [1.094–1.329], P <0.001) were associated with higher 30-day mortality in patients with sepsis (Table 3).

Thirty-day sepsis survivors (N = 205) were further included in Cox regression analysis for 3-year outcome. Diabetes (HR = 2.562 [1.209–5.431], P = 0.014), lung infection (HR = 3.411 [1.615–7.202], P = 0.001), admission qSOFA >1 (HR = 2.94 [1.373–6.296], P = 0.006) and unplanned ICU re-admission (HR = 5.251 [2.166–12.729], P <0.001) were associated with increasing 3-year mortality (Table 4).

Discussion

Incidence and mortality of sepsis varied in racial groups, and in different types of intensive care units, ranging from 18–30.2%.[8–10] Our study first reported a single center sepsis incidence of 16.6% in a combined medical and surgical high dependency/ ICU population in Singapore. It was close to the incidence of severe sepsis (sepsis-2 criteria) of 11.8% reported by Finfer et al. from Australia and New Zealand,[11] where the structure of intensive care units were similar, but

Table 2 Clinical Data of Sepsis Patients with Group Comparison

	Total N = 254	Septic Shock N = 141	Sepsis without Shock N = 113	P value	30 Day Survivor N = 205	30 Day Non-Survivor N = 49	P value
Site of infection							
Lung	106 (42%)	48 (34.0%)	58 (51.3%)	P<0.05	74 (36.1%)	32 (65.3%)	P<0.05
Abdomen	69 (27%)	44 (31.2%)	25 (22.1%)	P >0.05	60 (29.3%)	9 (18.4%)	P >0.05
Urinary tract	36 (14%)	20 (14.2%)	16 (14.2%)	P>0.05	33 (16.1%)	3 (6.1%)	P >0.05
Soft tissue	28 (11%)	21 (14.9%)	7 (6.2%)	P<0.05	24 (11.7%)	4 (8.2%)	P >0.05
Others	15 (6%)	8 (5.7%)	7 (6.2%)	P>0.05	14 (6.8%)	1 (2%)	P >0.05
[a]Length of stay before ICU admission (day)	0 (0–58)	0 (0–58)	0 (0–29)	0.403	0 (0–53)	0 (0–58)	0.001
qSOFA >1	83 (32.6%)	56 (39.7%)	27 (23.9%)	0.01	61 (29.8%)	22 (44.9%)	0.033
[a]SOFA score at ICU-admission	6 (2–17)	9 (2–17)	4 (2–9)	<0.001	5 (2–17)	9 (2–16)	<0.001
Invasive Mechanical Ventilation	89 (35%)	74 (52.5%)	15 (13.3%)	<0.001	55 (26.8%)	34 (69.4%)	<0.001
Positive blood culture	88 (34.6%)	56 (39.7%)	32 (28.3%)	0.038	73 (35.6%)	15 (30.6%)	0.314
[a]ICU Length of stay (day)	3 (1–35)	3 (1–35)	2 (1–14)	<0.001	3 (1–35)	4 (1–27)	0.037
Care Limitation/withdraw	19 (7.5%)	13 (9.2%)	6 (5.3%)	0.338			
Unplanned ICU readmission	17 (6.7%)	12 (8.5%)	5 (4.4%)	0.218			
30-day mortality	49 (19.3%)	39 (27.6%)	10 (8.8%)	<0.001			
1-year mortality	64 (25.2%)	49 (34.8%)	15 (13.3%)	<0.001			
2-year mortality	77 (30.3%)	56 (39.7%)	21 (18.6%)	<0.001			
3-year mortality	82 (32.3%)	59 (41.8%)	23 (20.4%)	<0.001			

Note: [a]Presented as median (Min-Max).
Abbreviations: ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; qSOFA, quick Sequential Organ Failure Assessment score.

lower than that reported in the MOSAICS study (25%).[4] Seasonal factors might play a role in sepsis incidence: winter was believed to have the highest incidence of sepsis,[12] while Singapore is a tropical country with little temperature variation throughout the year. Studies showed that higher temperature might be related to increasing incidence of nosocomial sepsis especially bloodstream infection,[13] and Gram-negative incidence increased by 13.1% for every 5°C increase in temperature.[14] Unfortunately, community- and hospital-acquired sepsis were not separately assessed in our study. Unit structure and case mix played a major part in discrepancy in sepsis incidence when compared with studies from the same region. Our lower Incidence was likely due to the number of post-elective procedure cardiac and surgical patients who contributed to the total admissions.

Our study firstly reported the severity of ICU sepsis in Singapore: 55.5% of sepsis patients had septic shock. Median admission SOFA score was 9 in septic shock patients and 4 in non-shock patients; 35% of sepsis patients required invasive mechanical ventilation. Like sepsis incidence, rate of septic shock was also highly associated with unit structure and case mix. The 30-day mortality of ICU sepsis in our study was 19.3%, with significant increase in patients with septic shock. MOSAICS study showed that in Asian ICUs, mortality of severe sepsis was lower in high-income countries, surgical ICUs, and units with an accredited fellowship program.[4] Our study showed risk factors associated with increasing 30-day mortality were older age, lung infection, immunocompromised host, and increasing admission

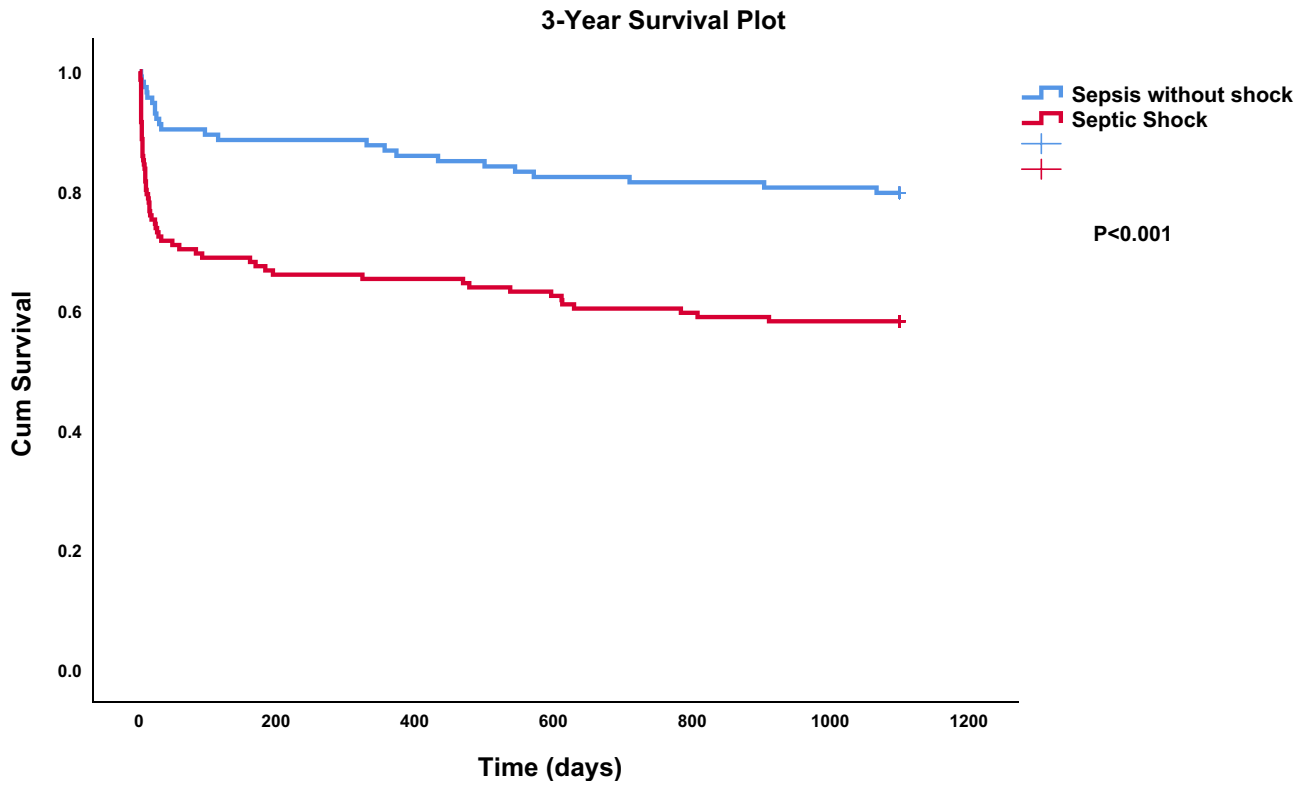

Figure 2 3-year survival plot comparing septic shock and sepsis without shock group.

SOFA score. These were similar to previous reports.[15,16] qSOFA score showed significance in relation to 30-day mortality in univariant analysis but not in multivariant analysis in our study.

Health-care associated infections such as ventilator-associated pneumonia, pressure injury, central line-associated bloodstream infection (CLABSI) and catheter-associated urinary tract infections (CAUTI) were known to be associated with increasing ICU mortality.[17] ICU-acquired sepsis was not assessed in our study but our unit implemented routine care bundles for prevention of ICU-associated sepsis. Future researches could be considered to assess in detail those complications which might burden ICU outcome. Our overall lower 30-day mortality compared with previous studies could be due to: (1) Study population: inclusive of high-dependency patients with lower SOFA score and post-operative surgical patients who had already achieved source control; (2) High bed capacity: our unit had a bed capacity of 34 and average bed occupancy rate was 70–80%. Practically, tight ICU bed capacity would result in relatively sicker patients being admitted leading to higher mortality.

Table 3 COX Regression Analysis for 30-Day Mortality

	HR	95% CI	P value
Age	1.028	1.005–1.051	0.010
Immunocompromised host	5.254	1.495–28.464	0.01
Lung infection	4.802	2.567–8.982	<0.001
Septic shock	2.054	0.837 −5.037	0.116
SOFA score at ICU admission	1.206	1.094–1.329	<0.001

Abbreviations: ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; HR, hazard ratio; CI, confidence interval.

Table 4 Cox Regression for 3-Year Mortality in 30-Day Survivors

	HR	95% CI	P value
Liver cirrhosis	4.493	0.992–20.359	0.051
Diabetes mellitus	2.562	1.209–5.431	0.014
Septic shock	2.348	0.883–6.245	0.087
Lung infection	3.411	1.615–7.202	0.001
ICU admission qSOFA>1	2.940	1.373–6.296	0.006
ICU admission SOFA score	0.89	0.761–1.040	0.142
Unplanned ICU readmission	5.251	2.166–12.729	<0.001

Abbreviations: ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; qSOFA, quick Sequential Organ Failure Assessment score; HR, hazard ratio; CI, confidence interval.

Long-term mortality data on ICU sepsis was not largely reported. Sepsis was shown to be an independent risk factor of long-term mortality specifically in first 2 years after hospital discharge, when compared with patients with infection but not septic (sepsis-2 criteria).[18] Our study showed significant long-term mortality of ICU sepsis in the first 2 years, with annual increment of 5–6%. Mortality at 3 years ramped up to 32.3% further, and it was higher in the septic shock group compared with non-shock group (41.8% vs 20.4%, P <0.001). However, overall long-term mortality in our study was lower than previous reports. A study from Finland reported 1-year mortality of ICU sepsis of 49%,[19] where the incidence of sepsis was only 3.8%. The 3-year mortality of ICU sepsis was reported as high as 55.4% in a single center cohort from Vienna.[20] Theoretically, long-term mortality of ICU sepsis would be affected by both patient and care factors —premorbid, origin and severity of acute illness, ICU treatment, hospital stay post ICU discharge and aftercare in the community. Unfortunately, none of the previous studies had included all these factors and neither did ours. Age, low body mass index (BMI) and diabetes were well-recognized risk factors associated with long-term mortality in ICU sepsis. Other factors seen in reports were ICU length of stay, mechanical ventilation and vital signs at ICU discharge.[21–23] Discharge to a rehabilitation facility was reported to improve 5-year survival in patients with sepsis and septic shock.[24] Our study showed increased 3-year mortality in 30-day survivors with increasing age, diabetes, lung infection and admission qSOFA score >1. There was a trend of increasing mortality in liver cirrhosis but this was not statistically significant (HR 4.493 [0.992–20.359], P = 0.051). The exceptionally low 3-year mortality in our study was likely due to factors contributing to low short-term mortality as discussed, and an established system of community aftercare in Singapore (hospital and private rehabilitation programs, home care facilities and day care services).

Similar to previous studies, lung was the most common site of infection.[11,25–27] Our study showed that lung infection was more frequently seen in sepsis patients without shock (51.3% vs 34%, P<0.05), but less in 30-day survivors (36.1% vs 65.3%, P<0.05). It suggested that respiratory failure was likely to be the predominant or even sole organ failure in patients with lung infection, especially when high dependency unit patients needing only non-invasive ventilation support were included in our study population, but it was associated with significant mortality. Whether patients with lung infection did worse than patients with other septic origins remains controversial. Two studies from China compared lung and abdominal sepsis; one showed lung infection was an independent risk factor for worse 1-year outcome and quality of life, while the other reported the complete opposite finding.[28,29] In our study, lung infection was shown to be associated with both increasing 30-day and 3-year mortality when compared with infection from a non-lung source.

Our study, using sepsis-3 criteria and looking through a large cohort of ICU patients admitted over 6 months where seasonal climate change is minimal, was the first detailed report of incidence, severity, short-term and long-term mortality in a combined medical and surgical high dependency/ ICU patient population in Singapore. Our study had certain limitations: Firstly, it was a retrospective cohort study and selection bias was unavoidable. Secondly, we only assessed incidence of sepsis at ICU admission, ICU-acquired recurrent sepsis was not included. Thirdly, detailed microbiology results and antimicrobials therapy were not available and these may affect the survival analysis.

Conclusion

Incidence of sepsis was 16.6% at admission in combined medical and surgical high dependency/ ICU population in Singapore, 55.5% of which had septic shock. The 30-day, 1-year, 2-year and 3-year mortality of sepsis was 19.3%, 25.2%, 30.3% and 32.3% respectively. These were lower than previous studies. Lung infection was an independent factor of increasing mortality at 30 days and 3 years.

Disclosure

The authors report no conflicts of interest in this work.

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