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MAJOR ARTICLE

Neutropenic Sepsis in the Intensive Care Unit: Differences in Clinical Profile and Outcomes According to the Cause of Neutropenia

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Background. Neutropenic sepsis frequently requires admission to an intensive care unit (ICU). Differences between subgroups of patients with neutropenic sepsis are not well characterized.

Aims. To investigate clinical outcomes among patients with neutropenic sepsis and hematological malignancy, metastatic solid cancer, or no cancer diagnosis.

Methods. Retrospective cohort study of all patients admitted to ICU in Australia or New Zealand between January 2000 and December 2022 with a primary admission diagnosis of sepsis and total white cell count $<1.0 \times 10^9$ cells/L.

Results. We identified 8617 ICU admissions with neutropenic sepsis (hematological malignancy n = 4660; metastatic solid cancer n = 1034; no cancer n = 2800). Patients with hematological malignancy were younger (median, 61.5 years) with low rates of chronic comorbidities (4.7%) and were usually admitted to ICU from the ward (67.4%). Mechanical ventilation rates were 20.2% and in-hospital mortality was 30.6%. Patients with metastatic solid cancers were older (median, 66.3 years), with higher rates of chronic comorbidities (9.9%), and were usually admitted to the ICU from the emergency department (50.8%). Mechanical ventilation rates were 16.9% and in-hospital mortality was 42.4%. Patients with no documented cancer had highest rates of mechanical ventilation (41.7%) and mortality (46.3%). Neutropenia was independently associated with mortality among patients with solid cancers or no cancer but did not confer increased risk among patients with hematological malignancy (odds ratio, 0.98; 95% confidence interval, .90–1.06; $P = .60$).

Conclusions. Patients with neutropenic sepsis and hematological malignancy, metastatic solid cancer, or no cancer diagnosis constitute 3 distinct clinical groups. Management approaches should be tailored accordingly.

Keywords. cancer; immunocompromised hosts; neutropenia; sepsis; supportive care.

BACKGROUND

Neutropenic sepsis is a frequent reason for admission to the intensive care unit (ICU). Mortality in neutropenic sepsis among patients requiring ICU admission has been reported at 30%–60% [1, 2], and healthcare costs for sepsis admissions are double that of other cancer-related admissions [3]. Estimates of neutropenic sepsis incidence are mostly extrapolated from studies of patients with malignancy, a group that account 16%–20% of ICU admissions with sepsis [2, 4, 5], and is continuing to grow [2, 6].

Management of neutropenic sepsis is an established priority for hospital safety and quality of care [7]. Most hospitals have guidelines emphasizing standardized management with rapid recognition and administration of antibiotics [7]. However, patients with neutropenic sepsis represent a diverse group and the epidemiology of neutropenic sepsis in ICU is incompletely characterized. Multicenter cohort studies have combined neutropenic and nonneutropenic cancer patients [2, 8] and those with other critical illness [1, 2, 9]. A more detailed understanding of the distinct cohorts of patients who develop neutropenic sepsis would help guide prognostication after initial emergency response and would guide future quality improvement targets.

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There are several knowledge gaps relating to the epidemiology of neutropenic sepsis. Existing studies of treatment and outcomes in neutropenic sepsis frequently group solid cancer and hematological malignancy together [8, 10–13]. However, these groups may not be comparable. Subgroup analysis suggests patients with hematological malignancy experience sepsis at higher rates than patients with solid cancers [3] but have better survival [14, 15]. Patients with neutropenia not related to malignancy or cancer therapy are seldom described.

Second, the contribution of neutropenia itself to overall sepsis outcomes is unclear. Studies of the impact of neutropenia on sepsis mortality have yielded conflicting results [1, 6, 16, 17], possibly related to heterogeneity of included patients. It may be that neutropenia has a differential impact on mortality risk in different patient subgroups.

Finally, neutropenic sepsis occurs within a rapidly changing clinical context. There have been significant advances in both cancer treatments and supportive care for patients with critical illness over the past 2 decades. In this time, cohort studies from Europe [8] and Australia [14] demonstrate improved outcomes in cancer patients admitted to the ICU [6], and those with sepsis [8] and septic shock [13]. However longitudinal trends in outcomes for patients with neutropenic sepsis have not been widely described.

AIMS

To describe the clinical characteristics, outcomes, and predictors of mortality in patients with neutropenic sepsis admitted to the ICU in Australia and New Zealand over the past 2 decades and compare those with hematological malignancy, metastatic solid cancer, or no cancer diagnosis.

METHODOLOGY

Study Design

Retrospective cohort study of all patients admitted to the ICU in Australia or New Zealand during the study period.

Ethics approval was obtained from the Alfred Health Ethics Advisory Group (Project number 292/20).

Data Collection

All patients admitted to an ICU at 1 of 223 centers in Australia and New Zealand between 1 January 2000 and 31 December 2022 were eligible for inclusion [18].

Data were extracted from the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD). The ANZICS-APD is an electronic database that collects episodes of care from ICUs in Australia and New Zealand, including patient demographics, primary diagnoses, comorbidities, physiological data from the first 24 hours of admission, mortality, and length of stay. The ANZICS-APD presently receives data on approximately 190 000 ICU admissions each year from 216 centers, representing 98% of all adult ICU admissions in Australia and 67% in New Zealand [18, 19]. Data reported to the ANZICS-APD are collected by trained staff in each participating ICU and validated by the Australian and New Zealand Intensive Care Society Centre for Outcome Evaluation through a variety of automated data quality processes and feedback to sites.

Definitions

Sepsis was defined as either (1) primary documented admission diagnosis of sepsis or (2) primary diagnosis of infection and organ dysfunction measured by Sequential Organ Failure Assessment (SOFA) score ≥2, as defined by the Third International Consensus Definitions for Sepsis and Septic Shock [20]. Primary ICU admission diagnoses were coded according to the ANZICS modification of the Acute Physiological and Chronic Health Evaluation (APACHE) diagnostic coding system [19]. Only 1 admission diagnosis was recorded.

Neutropenia was inferred from leukopenia, as defined as lowest or highest total white cell count (WCC) $< 1.0 \times 10^9$/L. This is in keeping with previous work and has high specificity for neutropenia (absolute neutrophil count $<0.5 \times 10^9$) [21–23].

Comorbid diagnoses of hematological malignancy (leukemia, myeloma, or lymphoma) or metastatic solid cancer were recorded for calculation of the APACHE scores.

Presence of other comorbidities was extracted from APACHE scores and required evidence of the diagnosis recorded at the time of ICU admission and meeting prespecified severity criteria as follows:

- Cardiovascular disease: New York Heart Association Class IV symptoms present at rest or minimal exertion
- Respiratory disease: severe exercise restriction or chronic hypoxia, hypercapnia, polycythemia, or pulmonary hypertension
- Liver disease: proven cirrhosis and portal hypertension or upper gastrointestinal bleed attributed to portal hypertension
- End-stage renal disease requiring hemodialysis or peritoneal dialysis
- Immunosuppression: presence of a disease sufficiently advanced to suppress resistance to infection (AIDS, severe autoimmune disease, leukemia, lymphoma, or metastatic solid cancer), or has received therapy that has suppressed resistance to infection (eg, immunosuppression, high-dose corticosteroids >1.5 mg/kg methylprednisolone for ≥ 5 days, long-term treatment with >20 mg/day prednisolone, chemotherapy within the past 4 weeks, radiation).

Illness severity scores including SOFA, APACHE-III, and Australia New Zealand Risk of Death (ANZROD) scores were calculated as previously described [24–26]. In-hospital

mortality was defined as death before discharge or transfer to another facility.

Presence of limitation of treatment order was coded as a binary variable. A limitation of treatment order refers to standardized forms within an institution or healthcare network used to document goals of care, established in discussion with the patient or their family. Limitations of treatment may include cardiopulmonary resuscitation, intubation, vasopressors, renal replacement therapy, or other treatments [27].

Inclusion Criteria

All patients aged ≥16 years with a primary ICU admission diagnosis of sepsis during the study period were considered for inclusion.

Only first admissions to the ICU were included. Readmission episodes and patients discharged to another ICU at a different site were excluded to avoid duplication. Patients were excluded if they were admitted to the ICU for palliative care or organ donation. Patients with missing data for WCC or hospital mortality data were excluded.

Statistical Analysis

Descriptive analysis of patient demographics, clinical characteristics, and outcomes was performed. Results were reported as n (%), mean (standard deviation), and median (interquartile range) as appropriate. For dichotomous variables, means with 95% confidence intervals (CI) calculated using binomial proportion were reported. Group comparisons were made using chi-square tests for equal proportion, Student *t*-test, or analysis of variance for normally distributed outcomes, and Wilcoxon-Mann-Whitney or Kruskal-Wallis tests otherwise.

To investigate mortality predictors a logistic regression model was fitted. Candidate variables were chosen solely on clinical relevance as previously described in the literature [9, 16] and included the following: age; sex; cancer type (hematological vs metastatic solid cancer); presence of comorbid cardiovascular, respiratory, liver, or renal disease; SOFA score (fitted as a categorical variable in quartiles); postoperative status; hospital classification type (tertiary, metropolitan, rural, or private); ICU admission source; mechanical ventilation; and year of admission. The final mixed model included only variables that were significant at a univariable level ($P < .001$) with patients nested within sites and site treated as a random effect. Formal assessment of collinearity was made by considering variance inflation with model plausibility validated by assessment and comparison of univariable and multivariable effect estimates. A mixed effects model was used with patients nested within sites and site treated as a random effect.

To quantify the impact of neutropenia on different cancer groups, a second model was fitted including all patients with a primary admission diagnosis of sepsis (with or without neutropenia). In this model, outcomes between neutropenic and nonneutropenic patients were compared and an interaction variable between neutropenia and cancer type was fitted to establish whether the impact of neutropenia differed between cancer groups.

All logistic regression results have been reported as odds ratios (ORs) and 95% CIs. Linearity between each continuous variable and the dependent variable was demonstrated. In case of nonlinearity, the variable was stratified based on inflection points and clinical significance. For categorical variables with multiple levels, the reference level was attributed to the one with the lowest probability of the dependent variable. The model was validated using the area under the receiver operating characteristic curve.

Analyses were performed using Stata version 18.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Between January 2000 and December 2022, there were 317 422 admissions to an ICU in Australia and New Zealand with a primary diagnosis of sepsis in patients aged ≥16 years. Of these, 57 884 were excluded (21 895 readmissions, 10 279 transfers to another ICU, 887 admitted for palliative care, 1734 with missing mortality data, 23 089 missing WCC data). There were 259 538 patient admission episodes included in the final analysis (Supplementary material: Supplementary Figure 1).

Neutropenia was present on admission in 8617/317 422 (3.3%) of all patients with sepsis. Among neutropenic patients, 4660 (54.1%) had a hematological malignancy, 1034 (12%) had metastatic solid cancer, 123 (1.5%) had both solid cancer and hematological malignancy, and 2800 (32.5%) had no recorded cancer diagnosis (Figure 1). Of those with no cancer diagnosis, 1283/2800 (45.8%) were recorded as having an immunosuppressing condition or receiving immunosuppressing treatment.

Data completeness was >99% for sex, age, SOFA, APACHE-II, APACHE-III, ANZROD scores, mechanical ventilation, and ICU length of stay; and >98% for hospital length of stay. Treatment limitation data were consistently collected from 2007 onward (>85% completeness after 2008). Vasopressor data were collected from 2017.

Clinical Characteristics of Neutropenic Sepsis in Patients With Hematological Malignancy, Solid Cancer, or no Malignancy

Clinical characteristics of patients with neutropenic sepsis admitted to the ICU are shown in Table 1. Patients with hematological malignancy, metastatic solid cancer, and no cancer differed in age, comorbidities, clinical presentation, and ICU admission source (emergency, ward, or other).

Patients with hematological malignancy were typically admitted to the ICU from the hospital ward (67.4%) and were most commonly admitted to the ICU in tertiary hospitals (68.7%). They were younger than patients with metastatic solid

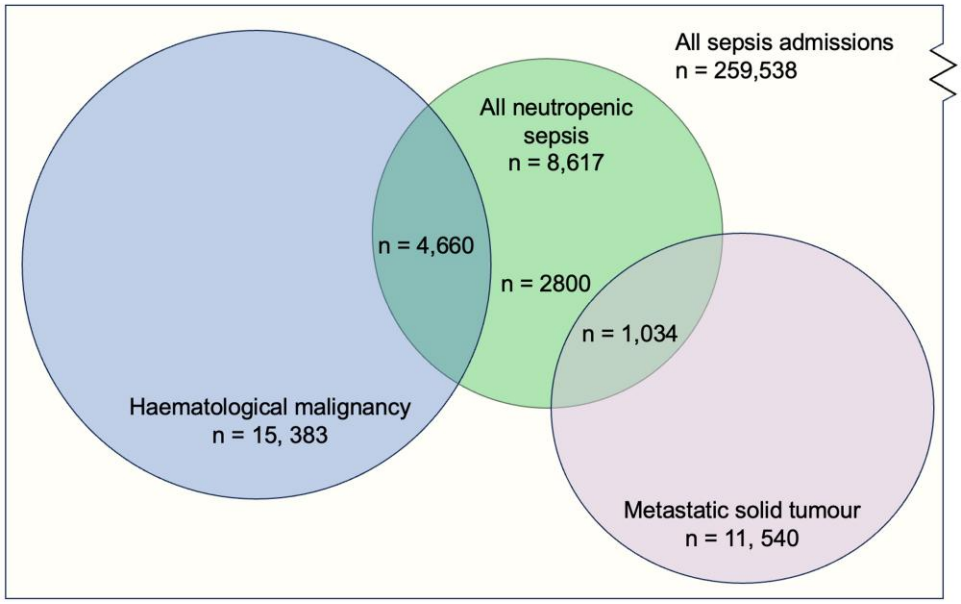

Figure 1. Neutropenic sepsis in patients with and without cancer admitted to the ICU in Australia and New Zealand 2000–2022. A total of 2800 patients had neutropenia and sepsis with no cancer diagnosis; 123 patients with both metastatic solid cancer and hematological malignancy not shown.

cancers (median, 61.5 years; interquartile range [IQR] 50.8–69.0 vs median 66.3 IQR 57.6–73.7) and had low rates of comorbidities (4.7%) and limitation of treatment orders (12%). Patients were mechanically ventilated in 20.2% of episodes. Neutropenia was profound (median WCC, 0.1; IQR 0.1–0.3) and peak temperature was high (38.2; IQR 37.4–39.0 vs median 37.7 IQR 37.0–38.4). In contrast, patients with solid cancers were most commonly admitted to the ICU from the emergency department (50.8%) and were less frequently admitted to the ICU in tertiary hospitals (36.1%). They had higher rates of chronic comorbidities (9.9%) and limitation of treatment orders (38.4%), but similar rates of mechanical ventilation (16.9%). Patients with no cancer diagnosis and no immunosuppression had modest neutropenia (median WCC, 0.5×10^9 cells/L) and very high rates of mechanical ventilation (46%).

Overall, 73% of patients with neutropenic sepsis received vasopressors during their ICU admission, with no significant difference between groups ($P = .21$).

Outcomes of Neutropenic Sepsis

Outcomes for patients with neutropenic sepsis admitted to the ICU are shown in Table 2. Patients with hematological malignancy had lowest mortality (30.6%) and highest likelihood of discharge home. (60.4%). Mortality was higher in patients with metastatic solid cancer (42.4%) and those with no cancer and no immunosuppression (46.3%). Length of stay in survivors was longest in patients with hematological malignancy.

Changes in crude mortality over the study period are shown in Figure 2. There was a significant decline in mortality in all patients over the study period. For patients with hematological malignancy mortality fell from 64.7% in 2000 (95% CI, 38.3–85.8) to 29.4% in 2022 (95% CI24.7–34.4). For patients with metastatic solid cancer, mortality fell from 71.4% (95% CI, 29.0–96.3) to 40% (95% CI, 30.6–50.4). Among those with no cancer, mortality fell from 66.7% (95% CI, 47.2–82.7) in 2000 to 39.1% (95% CI, 32.446.1%).

Predictors of Mortality and Impact of Neutropenia

Independent predictors of hospital mortality in patients with neutropenic sepsis are shown in Table 3.

In univariable and multivariable analysis, age, presence of ≥1 comorbidity, treatment limitation, year of ICU admission, and SOFA score were all associated with increased mortality ($P < .001$). Diagnosis of hematological malignancy and year of admission were associated with decreased risk of mortality ($P < .001$).

There was a significant interaction between neutropenia and cancer type. In multivariable analysis, neutropenia was associated with increased odds of death for patients with metastatic solid cancer (OR, 1.51; 95% CI, 1.30–1.74) and no cancer diagnosis (OR, 3.15; 95% CI, 2.89–3.43), but had no impact on mortality for patients with hematological malignancy (OR, 0.98; 95% CI, .90–1.06).

Sensitivity Analysis

Treatment limitation was excluded from the risk models because data collection was not routine until 2008. A sensitivity analysis was performed including treatment limitation order

Table 1. Demographic and Clinical Characteristics of Patients With Neutropenic Sepsis

					No Malignancy (n = 2800)			
	Hematological Malignancy (n = 4660)		Metastatic Solid Cancer (n = 1034)		Immunosuppression (n = 1283)		No Immunosuppression (n = 1517)	
	n	(%)	n	(%)	n	(%)	n	(%)
Male	2887	(62.0%)	582	(56.3%)	657	(51.2%)	869	(57.3%)
Age med (IQR)	61.5	(50.8, 69.0)	66.3	(57.6, 73.7)	63.5	(53.7, 71.6)	62.84	(50.3, 72.1)
Comorbidities[a]								
Cardiovascular disease NYHA class IV	82	(1.8%)	42	(4.1%)	50	(3.9%)	78	(5.1%)
Severe respiratory disease	77	(1.7%)	51	(4.9%)	57	(4.4%)	88	(5.8%)
Chronic liver disease	23	(0.5%)	14	(1.4%)	30	(2.3%)	48	(3.2%)
Dialysis	63	(1.4%)	18	(1.7%)	64	(5.0%)	53	(3.5%)
≥1 of the above	217	(4.7%)	102	(9.9%)	169	(13.2%)	221	(14.6%)
Treatment limitation[b]	491	(12.0%)	359	(38.4%)	160	(13.8%)	153	(12.4%)
Mechanical ventilation	939	(20.2%)	175	(16.9%)	359	(28.0%)	693	(45.7%)
Receipt of vasopressors[c]	1265	(74.0)	334	(73.7)	348	(69.5)	301	(71.7)
Risk stratification								
SOFA score, median (IQR)	8	(6, 10)	7	(5, 9)	7	(5, 10)	8	(6, 11)
APACHE II score, mean (SD)	26.2	(7.2)	27.1	(7.7)	28.9	(7.8)	27.1	(9.1)
APACHE III/IV score, mean (SD)	94.1	(26.4)	100.7	(27.2)	99.9	(29.7)	100.7	(33.2)
ANZROD score, median (IQR)	0.29	(0.13, 0.57)	0.35	(0.15, 0.66)	0.26	(0.10, 0.57)	0.33	(0.12, 0.67)
ANZROD score, mean (SD)	0.37	(0.28)	0.41	(0.29)	0.35	(0.29)	0.40	(0.31)
Hospital classification								
Rural	222	(4.8%)	157	(15.2%)	155	(12.1%)	192	(12.7%)
Metropolitan	635	(13.6%)	263	(25.4%)	237	(18.5%)	362	(23.9%)
Tertiary	3203	(68.7%)	373	(36.1%)	736	(57.4%)	801	(52.8%)
Private	600	(12.9%)	241	(23.3%)	155	(12.1%)	162	(10.7%)
ICU admission source								
OT/recovery	55	(1.2%)	18	(1.7%)	34	(2.7%)	58	(3.8%)
ED	1263	(27.1%)	524	(50.8%)	543	(42.3%)	694	(45.8%)
Ward	3136	(67.4%)	402	(39.0%)	607	(47.3%)	593	(39.1%)
Other[d]	202	(4.3%)	88	(8.5%)	99	(7.7%)	171	(11.3%)
Highest temperature, median (IQR)	38.2	(37.4, 39.0)	37.7	(37.0, 38.4)	37.8	(37.0, 38.7)	38.0	(37.1, 38.8)
Febrile >38.0 within 24 h of admission	2740	(58.8%)	442	(42.7%)	607	(47.3%)	797	(52.5%)
Lowest WCC, median (IQR)	0.1	(0.1, 0.3)	0.4	(0.2, 0.6)	0.4	(0.1, 0.6)	0.6	(0.2, 0.7)

Abbreviations: ANZROD, Australian and New Zealand Risk of Death; APACHE, Acute physiology and Chronic Health Evaluation; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; NYHA, New York Heart Association; OT, operative theater; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; WCC, white cell count.

A total of 123 patients with both hematological malignancy and metastatic solid cancer were excluded. All comparisons were significant $P < .001$, other than receipt of vasopressors ($P = .21$).

[a]Definitions per the APACHE-II coding system.

[b]Limitation of treatment data collected from 2007, n = 7,545.

[c]Vasopressor data collected from 2017, n = 3232.

[d]Other includes direct admission from home or hospital in the home.

data where available. In this model, mortality remained lower in hematological malignancy than the other groups (OR, 0.77; 95% CI, .68–.87; $P < .001$).

DISCUSSION

We analyzed 2 decades of binational data to describe clinical characteristics and outcomes of patients with severe neutropenic sepsis. To our knowledge, this is the largest observational study of patients with neutropenic sepsis admitted to the ICU. We observed that patients with hematological malignancy and metastatic solid cancers differed in clinical characteristics, outcomes, and source of ICU admission.

Patients with hematological malignancy were younger, with low rates of comorbidities and the lowest mortality of the group. Neutropenia in this group was not associated with increased mortality compared to nonneutropenic hematology patients with sepsis. In contrast, patients with solid cancers were older and had more comorbidities, with higher mortality, and neutropenia conferred an increased risk of death. Finally, patients with neither hematological malignancy nor metastatic solid cancer had high rates of mechanical ventilation and very

Table 2. Neutropenic Sepsis Outcomes

	Hematological Malignancy (n = 4660)		Metastatic Solid Cancer (n = 1034)		No Malignancy (n = 2800)			
					Other Immunosuppression (n = 1283)		No Immunosuppression (n = 1517)	
	n	(%)	n	(%)	n	(%)	n	(%)
Hospital outcome								
Death in hospital	1428	(30.6%)	438	(42.4%)	485	(37.8%)	702	(46.3%)
Death in the ICU	953	(20.5%)	320	(30.9%)	381	(29.7%)	597	(39.5%)
Discharged home	2815	(60.4%)	446	(43.1%)	619	(48.2%)	616	(40.6%)
Discharged to rehabilitation or long-term care facility	175	(3.8%)	49	(4.7%)	64	(5.0%)	66	(4.4%)
LOS in survivors								
LOS hospital days, median (IQR)	22.0	(10.6, 36.2)	11.2	(6.6, 20.9)	15.6	(7.6, 29.2)	20.0	(10.0, 34.3)
LOS ICU days, median (IQR)	2.6	(1.6, 4.9)	2.7	(1.7, 4.6)	3.0	(1.7, 5.9)	4.1	(1.9, 9.5)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.

A total of 123 patients with both hematological malignancy and metastatic solid cancer were excluded. All comparisons were significant $P < .001$.

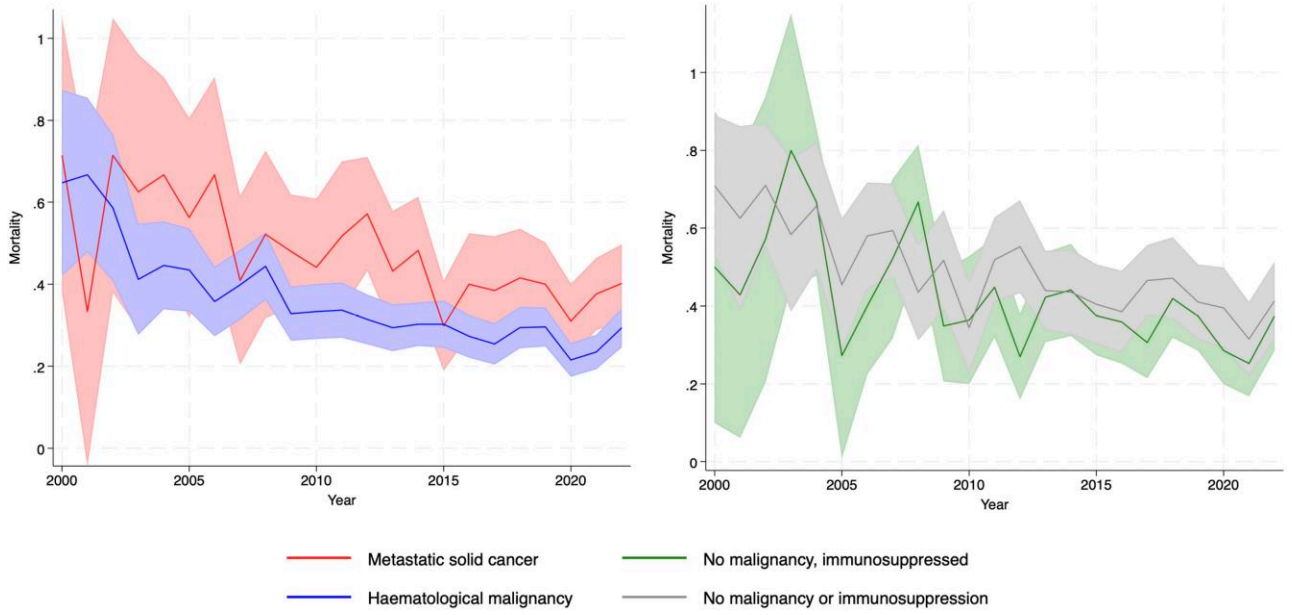

Figure 2. Hospital mortality in patients with neutropenic sepsis (mean ± 95% confidence interval) 2000–2022.

high hospital mortality. Neutropenia in the absence of hematological malignancy or metastatic solid cancer conferred a substantial increase in odds of death.

These findings add to a growing body of evidence suggesting favorable prognosis in patients with neutropenic hematological malignancy compared to other neutropenic patients with sepsis [14, 15]. A large cohort study performed in Korea reported lower mortality among hematology patients with neutropenic compared to nonneutropenic sepsis [11]. Neutropenia in patients with hematological malignancy is frequently a transient and predictable toxicity of cancer therapy and may be expected to resolve spontaneously or with growth factor administration. In addition, awareness of neutropenic sepsis and protocolized management may contribute to favorable outcomes. Conversely, our findings indicated that nonneutropenic sepsis in this group should not be underestimated. Importantly, in older or comorbid patients with hematological malignancy, high-intensity chemotherapy regimens associated with profound and prolonged neutropenia might be avoided in favor of reduced-intensity regimens. These patients may experience substantial immunosuppression

Table 3. Predictors of Neutropenic Sepsis Mortality

	Univariable			Multivariable		
	OR	(95% CI)	*P*	OR	(95% CI)	*P*
Male sex	1.01	(.93–1.11)	.70		…	
Age	1.02	(1.01–1.02)	<.001	1.02	(1.02–1.03)	<.001
≥1 chronic comorbidity[a]	1.98	(1.70–2.31)	<.001	1.59	(1.32–1.90)	<.001
Mechanical ventilation	5.29	(4.77–5.87)	<.001	3.59	(3.18–4.05)	<.001
SOFA score quartile	…	…	<.001		…	<.001
Q1 (reference)	-	-		-	-	
Q2	1.78	(1.32–2.39)		1.73	(1.27–2.35)	
Q3	2.84	(2.14–3.76)		2.73	(2.04–3.66)	
Q4	10.10	(7.72–13.21)		7.73	(5.83–10.25)	
Postoperative status	0.71	(.46–1.09)	.11	-	-	-
Hospital classification	…	…	NS		…	
Rural (reference)	–	-	–	-	-	-
Metropolitan	1.04	(.87–1.25)	.65	-	-	-
Tertiary	0.95	(.81–1.12)	.57	-	-	-
Private	1.07	(.88–1.29)	.50	-	-	-
ICU admission source	…	…	NS		…	
Operating theater (reference)	-	-	-	-	-	-
Emergency	0.95	(.69 -1.33)	.79	-	-	-
Ward	1.11	(.80–1.54)	.53	-	-	-
Other	1.35	(.94–1.93)	.11		…	
Year of admission (continuous)	0.95	(.94–.96)	<.001	0.96	(.95–.97)	<.001
Cancer type	…	…			…	
No malignancy (reference)	-	-	-	-	-	–
Hematological malignancy	0.60	(.54–.661)	<.001	0.78	(.69–.87)	<.001
Metastatic solid cancer	1.00	(.86–1.15)	.99	1.54	(1.30–1.82)	<.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; NS, not significant; OR, odds ratio; SOFA, Sequential Organ Failure Score.

A total of 123 patients with both hematological malignancy and metastatic solid cancer were excluded. Model area under the receiver operating characteristic curve = 0.76.

[a]Chronic comorbidities = chronic cardiovascular, respiratory, renal, or liver disease.

without neutropenia and may not be captured by the current study. Finally, poor outcomes in patients with solid cancer have also been previously reported [14, 15, 23] and may be partly explained by higher age, higher rates of comorbidities, and poorer cancer prognosis.

Patients with neutropenic sepsis and no recorded cancer diagnosis are a group of interest. Two single-center studies have previously examined neutropenic sepsis in noncancer patients in the ICU. In these studies, patients without cancer accounted for at least 5%–10% of all patients with neutropenic sepsis and the authors reported increased mortality and high levels of inflammatory biomarkers [28, 29]. This suggests neutropenia in noncancer patients to be a marker of severe sepsis. In our study, the proportion of patients with neither metastatic solid cancer nor hematological malignancy was higher (24% overall). This may reflect a more diverse group including patients with alternative causes for neutropenia, including immunosuppressive drugs for autoimmune disease or transplantation, and chemotherapy used in nonmetastatic solid cancer.

These findings have important implications for clinical care of patients with neutropenic sepsis. For patients with hematological malignancy, recognition of good prognosis may help guide rapid escalation of care, which has been associated with reduced mortality [30]. Conversely, our findings emphasize the clinical importance of nonneutropenic sepsis: 70% of patients with hematological malignancy and sepsis had normal neutrophil count, and this group had similar mortality to those with neutropenic sepsis. This group is at risk of being overlooked in neutropenic sepsis guidelines and quality initiatives. Most of these patients were admitted to the ICU from the ward, indicating that the target group for education or quality improvement are ward doctors, nurses, and medical emergency teams.

Among patients with metastatic solid cancers, advance planning for those with poor prognosis is important. In this cohort, one third had a treatment limitation order in place and hospital mortality was 40%; however, a majority of patients were admitted to ICU directly from the emergency department. This indicates the importance of patient education and care planning while the patient is well because the opportunity for these discussions may be limited when the patient develops sepsis.

Finally, neutropenic sepsis in the absence of hematological malignancy or metastatic solid cancer requires further study. This groups represented <1% of all patients with sepsis in our cohort but 24% of patients with neutropenic sepsis. It is likely that they represent a diverse group, and dedicated study of their clinical

characteristics and outcomes is needed. We hypothesize that in patients with no cancer diagnosis who are not receiving immunosuppression, neutropenia may reflect severe sepsis.

High in-hospital mortality for all groups highlights the importance of efforts to prevent neutropenic sepsis, and support of prompt recognition and early management including patient and carer education. Groups at high risk such that may be overlooked include nonneutropenic sepsis in hematology patients and neutropenia in noncancer patients.

This study has several strengths. To our knowledge, this is the largest published cohort study of neutropenic sepsis and includes comprehensive binational data from more than 200 ICUs. The study size and high levels of data completeness improves the generalizability of our findings. Our study also has limitations. We included all patients with a primary ICU admission diagnosis of sepsis; this approach may underrepresent clinical sepsis in patients admitted with multiple medical complications and those who develop sepsis after admission to ICU. Additionally, we extrapolated neutropenia from WCC, an indirect measure, though one that has been previously applied in similar studies [21, 23]. This metric has high specificity for neutropenia but limited sensitivity [22]. Additionally, neutropenia was considered as a binary outcome in this study, and we were unable to assess the impact of depth or duration of neutropenia. The Infectious Diseases Society of America guidelines identify duration of neutropenia as risk factors for fever [31]. However, this is based on expert opinion, and there is little evidence to quantify the risk of different neutropenic profiles on either sepsis risk, or mortality in those who develop sepsis [21, 32]. This is an area of need for future research.

The use of illness severity scores to control for severity of sepsis also presents a challenge because no critical illness severity score is well validated in cancer patients. SOFA score was selected for inclusion in our model based on better performance than APACHE II/III/IV [33–36]. In addition, other illness severity scores such as APACHE and Simplified Acute Physiology Score include WCC and/or cancer diagnosis in their calculation, which leads to collinearity and bias in analyses of neutropenic cancer patients. SOFA score only partly addresses this concern because the calculation includes platelet count, which is likely to correlate strongly with WCC. There is a need for dedicated critical illness scoring systems in cancer patients both for prognosis and to facilitate more accurate analysis of outcomes.

Finally, we did not capture clinical data on patients with solid organ cancers that have not metastasized. Therefore, patients receiving neoadjuvant or adjuvant chemotherapy for early-stage tumors are not captured by this dataset. These patients may also have different clinical characteristics to those with metastatic disease.

CONCLUSION

Among patients with neutropenic sepsis, hematological malignancy, metastatic solid cancers, and other causes of neutropenia represent distinct clinical groups. Efforts to improve outcomes in neutropenic sepsis should be tailored for each group.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. A. M. contributed to study conception, data analysis, manuscript drafting, and revisions. C. D. contributed to interpretation of analysis and manuscript revisions. M. S. contributed to interpretation of analysis and manuscript revisions. R. W. contributed to study conception, interpretation of analysis, and manuscript revisions. M. B. provided oversight of statistical analysis and contributed to manuscript revisions. D. P. contributed to study conception, interpretation of analysis, manuscript revisions, and supervision. Z. M. contributed to study conception, interpretation of analysis, manuscript revisions, and supervision.

Patient consent statement. Ethics approval was obtained from the Alfred Health Ethics Advisory Group with a waiver of informed consent (Project number 292/20).

Data sharing statement. Access to information from ANZICS CORE is restricted due to confidentiality requirements pertaining to the use of clinical quality registry data in Australia and New Zealand. Specific requests may be considered on a case by case basis. Enquiries can be made to anzics.core@anzics.com.au.

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