Infection and Drug Resistance

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

# Impact of Infection Patterns on the Outcomes of Patients with Hematological Malignancies in Southwest China: A 10-Year Retrospective Case-Control Study

Yali Yang[1,*], Junjie Li[2,*], Shifeng Huang[1], Junnan Li[3], Shuangshuang Yang[1]

[1]Department of Laboratory Medicine, the First Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China; [2]Key Laboratory of Laboratory Medical Diagnostics, Ministry of Education, Department of Laboratory Medicine, Chongqing Medical University, Chongqing, People's Republic of China; [3]Department of Hematology, the First Affiliated Hospital of Chongqing Medical University, Chongqing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shuangshuang Yang, Department of Laboratory Medicine, the First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing, 400016, People's Republic of China, Tel +86-23-8901-1841, Fax +86-23-8901-2513, Email yangss2019@hospital.cqmu.edu.cn

**Background:** This study aimed to assess the effect of infection patterns on the outcomes of patients with hematological malignancies (HM) and to identify the determinants of in-hospital mortality.

**Methods:** A case-control study was retrospectively conducted in a tertiary teaching hospital in Chongqing, Southwest China from 2011 to 2020. Clinical characteristics, microbial findings, and outcomes of HM patients with infections were retrieved from the hospital information system. Chi-square or Fisher's exact test was adopted to test the significance of mortality rate. Kaplan-Meier survival analysis and Log rank test were applied to evaluate and compare the 30-day survival rates of those groups. Binary logistic regression, Cox proportional hazards regression, and receiver operating characteristic curves were used to investigate the determinants of in-hospital mortality.

**Results:** Of 1,570 enrolled participants, 43.63% suffered from acute myeloid leukemia, 69.62% received chemotherapy, and 25.73% had hematopoietic stem cell transplantation (HSCT). Microbial infection was documented in 83.38% of participants. Co-infection and septic shock were reported in 32.87% and 5.67% of participants, respectively. Patients with septic shock suffered a significantly lower 30-day survival rate, while those with distinct types of pathogens or co-infections had a comparable 30-day survival rate. The all-cause in-hospital mortality was 7.01% and higher mortality rate was observed in patients with allo-HSCT (7.20%), co-infection (9.88%), and septic shock (33.71%). Cox proportional hazards regression illustrated that elderly age, septic shock, and elevated procalcitonin (PCT) were independent predictors of in-hospital mortality. A PCT cut-off value of 0.24 ng/mL predicted in-hospital mortality with a sensitivity of 77.45% and a specificity of 59.80% (95% CI = 0.684–0.779, $P<0.0001$).

**Conclusion:** Distinct infectious patterns of HM inpatients were previously unreported in Southwest China. It was the severity of infection, not co-infection, source of infection, or type of causative pathogen that positively related to poor outcome. PCT guided early recognition and treatment of septic shock were advocated.

**Keywords:** early survival, hematological malignancies, in-hospital mortality, microbial co-infection, septic shock, determinants

## Introduction

Microbial Infection has been well documented as one of the most common complications for patients with hematological malignancies (HM) receiving chemotherapy or hematopoietic stem cell transplantation (HSCT) treatment.[1] However, the latest systematic reviews focusing on hematological malignancies (HM) and microbial infection have illustrated that the bulk of clinical trials present incomplete information of infections without indicating the type of pathogens or source of

Received: 21 February 2023
Accepted: 25 May 2023
Published: 8 June 2023



© 2023 Yang et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

infections,[2] or simply referred to individual microbials in neutropenic patients,[3] which rarely provided a structured presentation. In addition, due to the administration of vaccinations[4,5] and antibiotic prophylaxis,[6–8] the burden of microbial infection in HM patients may be alleviated. However, there is a paucity of studies concerning this alleviation in China.

Furthermore, microbial infection has been frequently related to higher mortality,[9,10] while its effect on the outcomes of HM patients has been complicated by the heterogeneity of malignancies,[11] type of pathogens,[12] and co-infections.[13] A recent intensive care study involving HM patients with sepsis indicated that patients with acute myeloid leukemia (AML) had a lower 90-day survival rate than those with other types of acute leukemia[14] and further research identified that fungi were the greatest contributor to the poor outcome of patients with AML than other causative pathogens.[15] Latest longitudinal studies in China and France have found a positive association of co-infection with higher mortality,[10,13,16] while a multi-center analysis focusing on cancer participants with fever and neutropenia declared no significant difference in the mortality rate between bacterial infection and viral-bacterial co-infection.[17] Accordingly, detailed investigations of the heterogeneity of malignancy and infection would allow a better understanding of the impact of infectious complications on the outcomes of HM patients. However, sparse data is referring to this heterogeneity in China.

To this end, we initiated a 10-year longitudinal study in HM inpatients that developed infections during chemotherapy or HSCT, to elucidate the difference of outcomes between HM inpatients with distinct types of malignancies, infection profiles, and treatments. The potential association of HM classification, infection profiles, and treatments with outcomes was investigated and the predictors of in-hospital mortality were further determined.

# Materials and Methods

## Study Design

A case-control study was retrospectively conducted in the hematology department of the First Affiliated Hospital of Chongqing Medical University from 2011–2020. Approval was obtained from the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (NO.2022-K336). Consent from patients was exempted by the IRB due to the retrospective nature of the study and the data of patients was anonymized or maintained with confidentiality and compliance with the Declaration of Helsinki. Cases were defined as HM inpatients who died during hospitalization and controls as patients who survived when discharged from hospital. The flowchart of participant enrollment is illustrated in Figure 1.

## Data Collection and Enrollment Criteria

Data of patients' age, gender, length of hospital stay (LOS), clinical diagnosis, treatments, source of infection, laboratory findings of microbial infections, etc. were retrieved from medical charts and laboratory information systems. All the positive laboratory microbial results of inpatients in hematological departments were recorded. Inpatients were enrolled if their records contained all the relevant information, including patients' age (over 14 years old), gender, unique patient identification number, diagnosis of hematological malignancies, type of infections, and treatments (chemotherapy, HSCT, or palliative treatment). As to laboratory findings, only the first identified pathogen was recorded if the same pathogen was isolated or determined in later checks, at 7 or 14 days. Co-infection was recorded if more than one pathogen was reported during hospitalization.[18]

## Definitions

Hematological malignancy was classified by clinical diagnosis. To reduce bias, a given malignancy with less than 200 cases was exempt from regression analysis.

Infection was generally defined by the consensus of clinical evidence and laboratory microbiological evidence from culture, molecular diagnosis, or serum tests. Given the failure of consensus, clinical diagnosis of infection was considered the top priority.

Septic shock was defined according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[19] Catheter-associated bloodstream infection was defined according to clinical practice guidelines for the

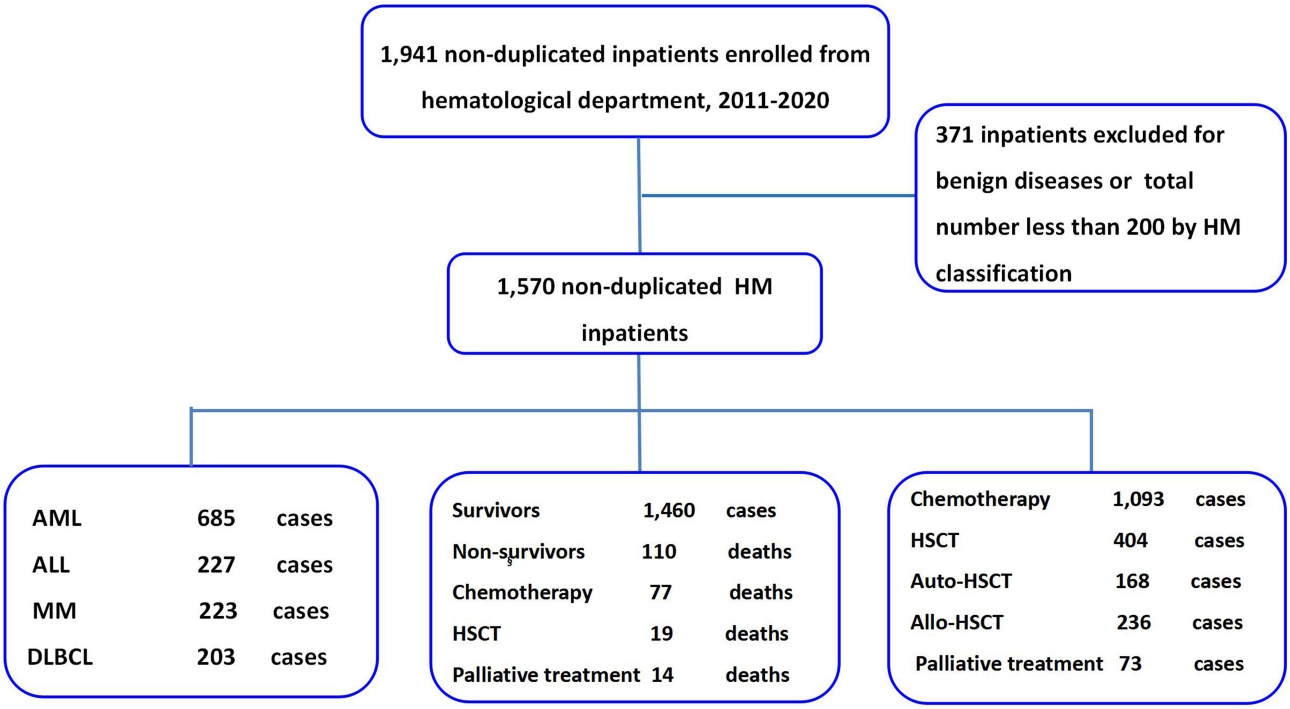


**Figure 1** Flowchart of the enrollment of HM inpatients in this study.
**Abbreviations**: HM, Hematological malignancy; AML, Acute myeloid leukemia; DLBCL, Diffuse large B-cell lymphoma; ALL, Acute lymphocytic leukemia; MM, Multiple myeloma; HSCT, Hematopoietic stem cell transplantation; Auto-HSCT, Autogenetic hematopoietic stem cell transplantation; Allo-HSCT, Allogeneic hematopoietic stem cell transplantation.

diagnosis and management of intra-vascular catheter-related Infection: 2009 Update by the Infectious Diseases Society of America.[20]

Invasive fungal infection (IFI) was defined according to the Official American Thoracic Society Clinical Practice Guidelines of Microbiological Laboratory Testing in the Diagnosis of Fungal Infections in Pulmonary and Critical Care Practice and European guidelines for primary anti-fungal prophylaxis in adult hematology patients,[21] and only probable or proven IFI was included in this cohort.

The primary outcome was the in-hospital mortality. The secondary outcome was the survival rate at 30 days after admission.

## Statistical Analysis

Descriptive statistics was adopted to calculate the demographic, clinical diagnosis, treatments, and infection-related patients' features. Continuous variables were evaluated for linearity in functional form. Chi-square test or Fisher's exact test was used to compare the distribution of mortality. Binary logistic regression analysis and Cox regression analysis were conducted to explore the associations of all potential predictors with mortality. Kaplan-Meier plots, Log rank test, or Gehan-Breslow-Wilcoxon Test[22] were generated to assess survival distributions based on patient characteristics of interest. SPSS 21 and Graphpad Prism 8 were applied to fulfill these statistics. The two-sided *P*-value of no more than 0.05 was considered statistically significant.

# Results

## Demographics

During this 10-year investigation period, 1,570 HM inpatients suffered infections and were enrolled in this cohort. The median age was 52 years old and 53.57% (841/1,570) were males. Acute myeloid leukemia (AML) was the most common malignancy and predominant in 43.63% (685/1,570) of participants, followed by acute lymphocytic leukemia

(ALL, 227/1,570, 14.46%), multiple myeloma (MM, 223/1,570, 14.20%), and diffuse large B-cell lymphoma (DLBCL, 203/1,570, 12.93%). Chemotherapy was the most frequent treatment and was adopted by 1,093 participants. Hematopoietic stem cell transplantation (HSCT) was performed in 404 participants, with 58.42% (236/404) of allogeneic HSCT (allo-HSCT) receipts. Apart from curative treatments, palliative treatment was undergone among 73 participants.

## Infection Profiles

As to infection sources, bloodstream infection (BSI) was predominant in 22.36% (351/1,570) of participants (Table 1), followed by respiratory infection (RPI, 133/1,570, 8.47%), urinary tract infection (UTI, 94/1,570, 5.99%), gut infection (77/1,570, 4.90%), and skin and soft tissue infection (SSTI, 62/1,570, 3.95%). Among 351 BSI, 14 cases were confirmed to be catheter-associated BSI, with an incidence of 0.89% (14/1,570) and 89 cases were reported as septic shock (89/1,570, 5.67%).

In regard of causative pathogens, bacteria were predominant in almost all sources of infection, except for SSTI (Figure 2A). Typically, *Escherichia coli* was the most frequent isolate from BSI and UTI, while *Haemophilus influenzae* and *Salmonella spp*. were prevalent in RPI and GI, respectively (Figure 2B). In contrast to bacteria, fungi were less common and a majority of them were *Candida Spp*. and were isolated from oral, sinusal, naso-pharyngeal, and gut mucosal infections. Proven invasive fungal infections (34/1,570, 2.17%) were sporadically distributed into 21 cases of

**Table 1** Characteristics of HM Inpatients with Infections from 2011–2020

| Variables | Overall | Survivors | Non-Survivors | *P*-values | Binary Regression Analysis | |
|---|---|---|---|---|---|---|
| | | | | | ORs (95% CIs) | *P*-values |
| **Total** | 1,570 | 1,460 | 110 | | | |
| Age, years (median, IQR) | 52 (35–63) | 51 (35–63) | 60(45–69) | <0.0001 | 1.032 (1.016–1.048) | 0 |
| Male | 841 (53.57%) | 769 (52.67%) | 72 (65.45%) | 0.015 | 1.453 (0.906–2.33) | 0.121 |
| LOS (median, IQR) | 29 (17–43) | 29 (17–43) | 25 (16–44) | 0.362 | | |
| **Malignancies** | | | | 0.47 | | |
| AML | 685 (43.63%) | 641 (43.90%) | 44 (40.00%) | 0.486 | | |
| ALL | 227 (14.46%) | 210 (14.38%) | 17 (15.45%) | 0.7581 | | |
| MM | 223 (14.20%) | 214 (14.66%) | 9 (8.18%) | 0.0652 | | |
| DLBCL | 203 (12.93%) | 188 (12.88%) | 15 (13.64%) | 0.7694 | | |
| **Microbial infections** | | | | 2.684 | | |
| Bacterial | 1,139 (72.55%) | 1,058 (72.47%) | 81 (73.64%) | 0.0703 | | |
| Fungal | 554 (35.29%) | 504 (34.52%) | 50 (45.45%) | 0.0207 | 2.026 (1.283–3.198) | 0.002 |
| Viral | 138 (8.79%) | 130 (8.90%) | 8 (7.27%) | 0.5601 | | |
| Co-infection | 516 (32.87%) | 465 (31.85%) | 51 (46.36%) | 0.018 | 1.101 (0.069–1.756) | 0.688 |
| **Infection sites** | | | | 0.167 | | |
| Bloodstream | 351 (22.36%) | 326 (22.33%) | 25 (22.73%) | 0.9229 | | |
| Respiratory tract | 133 (8.47%) | 120 (8.22%) | 13 (11.82%) | 0.1911 | | |
| Urinary tract | 94 (5.99%) | 92 (6.30%) | 2 (1.82%) | 0.059 | | |
| Gut | 77 (4.90%) | 71 (4.86%) | 6 (5.45%) | 0.7818 | | |
| **Clinical treatments** | | | | < 0.0001 | | |
| Palliative treatment | 73 (4.65%) | 59 (4.04%) | 14 (12.73%) | 0.0003 | – | – |
| Chemotherapy | 1,093 (69.62%) | 1,016 (69.59%) | 77 (70.00%) | 1 | | |
| HSCT | 404 (25.73%) | 385 (26.37%) | 19 (17.27%) | 0.0411 | | |
| Auto-HSCT | 168 (10.70%) | 166 (11.37%) | 2 (1.82%) | 0.0006 | 1.352 (0.959–1.907) | 0.085 |
| Allo-HSCT | 236 (15.03%) | 219 (15.00%) | 17 (15.45%) | 0.8901 | | |
| Septic shock | 89 (5.67%) | 59 (4.04%) | 30 (27.27%) | < 0.0001 | 12.246 (6.718–22.324) | 0 |
| PCT (median, IQR) | 0.19 (0.08–0.62) | 0.17 (0.07–0.53) | 0.74 (0.26–3.75) | 0.005 | 1.026 (1.007–1.046) | 0.008 |

**Abbreviations**: HM, Hematological malignancy; IQR, Interquartile range; OR, Odds ratio, CI, Confidence Interval, LOS, Length of hospital stay; AML, Acute myeloid leukemia; DLBCL, Diffuse large B-cell lymphoma; ALL, Acute lymphocytic leukemia; MM, Multiple myeloma; HSCT, Hematopoietic stem cell transplantation; Auto-HSCT, Autogeneic hematopoietic stem cell transplantation; Allo-HSCT, Allogeneic hematopoietic stem cell transplantation; PCT, Procalcitonin.

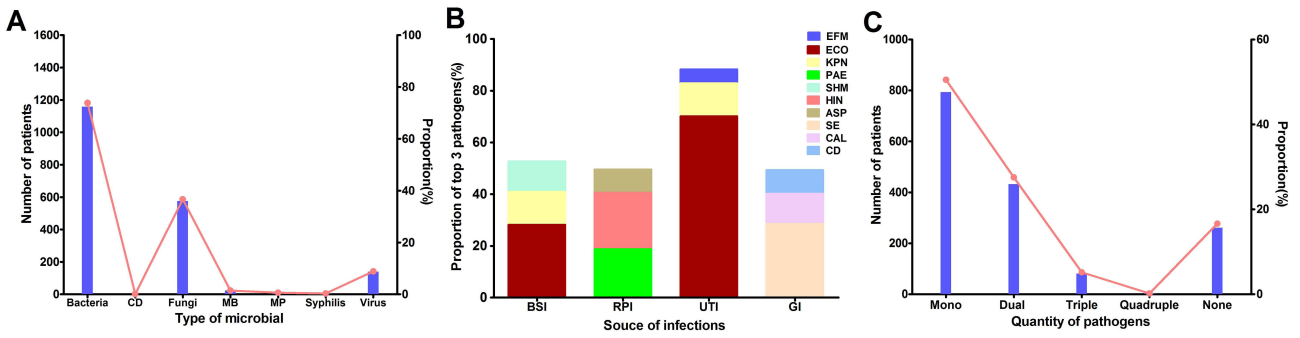


**Figure 2** The infection profiles of HM inpatients. Distribution of (**A**) microbial, (**B**) top three causative pathogens isolated from distinct sources of infections (**C**) infections by distinct quantities of causative pathogens.

**Abbreviations**: BSI, Bloodstream infections; RPI, Respiratory infections; UTI, Urinary tract infections; GI, Gut infections; CD, *Clostridium difficile*; MB, *Mycobacterium*; MP, *Mycoplasma*; EFM, *Enterococcus faecium*; ECO, *Escherichia coli*; KPN, *Klebsiella pneumoniae*; PAE, *Pseudomonas aeruginosa*; SHM, *Staphylococcus hominis*; HIN, *Hemophilus influenzae*; ASP, *Aspergillus fumigatus*; SE, *Salmonella enteritidis*; CAL, *Candida albicans*.

candidemia, 12 cases of proven invasive pulmonary aspergillosis, and one case of disseminated cryptococcosis. Unlike bacteria and fungi, viruses were frequently reported in SSTI, with the predominance of herpes viruses (33/62, 53.23%).

As to type of infection (Figure 2C), among 1,570 participants, more than half (793/1,570) of them suffered mono-microbial infection, 32.87% (516/1,570) had co-infection, and 261 participants failed to report any causative pathogens by laboratory findings. Of note, dual infection by bacteria-fungi was the most common co-infection, taking a high proportion of 73.84%.

## Outcomes

The early outcome of this cohort was the survival rate at 30 days after admission. As shown in Figure 3, more than 90% of participants survived in the early 30-day admission, regardless of malignancies (Figure 3A), treatments (Figure 3B), or quantities of microbial infections (Figure 3C), while participants with septic shock suffered a dramatically lower 30-day survival rate than those without septic shock (80.22% vs 96.27%, $P<0.0001$, Figure 3D).

The primary outcome of all-cause in-hospital mortality of this cohort was 7.01% (110/1,570), altered with quantity of microbial infection and severity of infection, but not type of malignancy, treatment or source of infection (Figure 4). As to malignancy, participants with ALL seemed to suffer a high mortality rate of 7.49% (17/227), in contrast to those with other investigated malignancies, while Chi-square test failed to detect this difference ($P=0.47$, Figure 4A). In regard of treatment, participants with palliative treatment reported a remarkably higher in-hospital mortality rate of 19.18% (14/73) than those undertaking chemotherapy (77/1,093, 7.04%) or HSCT (19/404, 4.70%) ($P<0.0001$, Figure 4B). Interestingly, although participants who had undertaken chemotherapy seemed to have a higher mortality rate than HSCT recipients, this difference was insignificant. Subgroup analysis further suggests allo-HSCT recipients had a substantially higher mortality rate than auto-HSCT receipts (7.20% vs 1.19%, $P=0.004$).

Despite participants with respiratory infections and those with fungal infections suffering a high mortality rate of more than 9%, subgroup analysis found a comparable mortality rate between those with different types of pathogens or sources of infections (Figure 4C and D). Interestingly, participants with co-infection suffered a remarkably high in-hospital mortality rate, in contrast to those with mono-infection, and dual infection contributed a lot to it (9.88% vs 6.07%, $P=0.01$, Figure 4E). Noticeably, a significantly high mortality rate of 33.71% was found among participants with septic shock, in contrast to those without septic shock of 5.4% ($P<0.0001$, Figure 4F).

## Predictors for in-Hospital Mortality

Clinical and microbiological findings of survivors and non-survivors during hospitalization are illustrated in Table 1. Binary regression analysis indicated that elderly age, fungal infection, septic shock and elevated procalcitonin (PCT) were positively associated with in-hospital mortality, while source of infection or co-infection were not related with this poor outcome. It is worth noting that, after the adjustment of length of hospital stay by Cox regression analysis, the

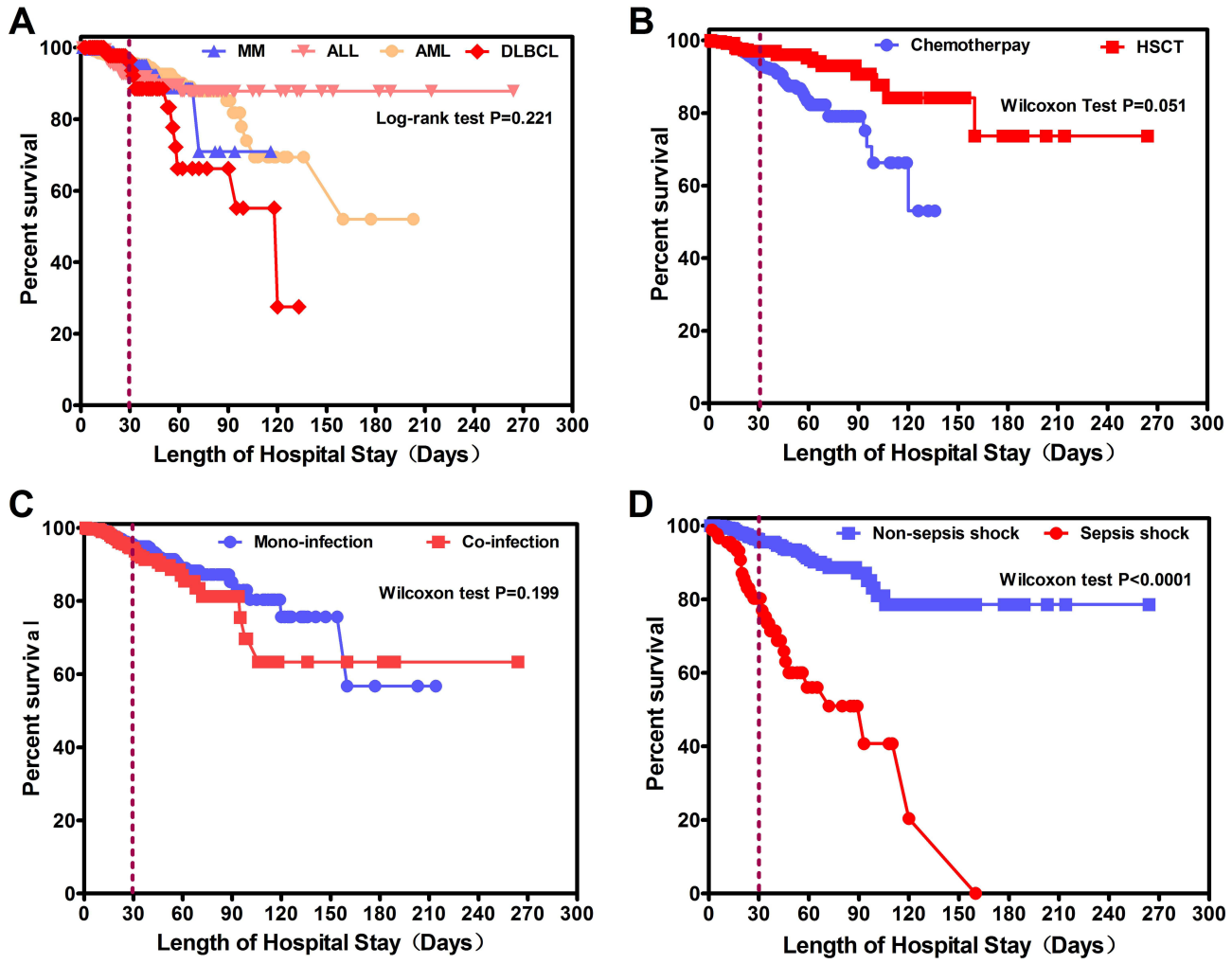


**Figure 3** Survival curves by (**A**) hematological malignancies, (**B**) treatments, (**C**) quantity of causative pathogens, and (**D**) severity of infection. Differences between these groups were assessed by using Log rank test and Wilcoxon test.

**Abbreviations**: AML, Acute myeloid leukemia; DLBCL, Diffuse large B-cell lymphoma; ALL, Acute lymphocytic leukemia; MM, Multiple myeloma; HSCT, Hematopoietic stem cell transplantation.

positive relevance of fungal infection and mortality rate in binary regression analysis was dissolved, leaving elder age, septic shock, and elevated PCT as the independent predictors of in-hospital mortality (Figure 5A). Moreover, ROCs finally illustrated that PCT predicted mortality with an area of 0.73 under the curve (95% CI = 0.684–0.779, $P<0.0001$). A cut-off point of 0.24 ng/mL provided a sensitivity of 77.45% and a specificity of 59.80% (Figure 5B).

## Discussion

This study presented the current available information of infection profiles and outcomes of HM inpatients during chemotherapy or HSCT treatment in Southwest China. Our findings verified the distinct infection profiles and the heterogeneity of the impact of co-infection, severity of infection, type of malignancy, and treatment on the outcome of HM inpatients in the infection context.

Consistent with previous studies,[12,23,24] microbial infection was documented in 83.38% of HM inpatients. *Escherichia coli* and bloodstream were the predominant causative pathogen and source of infection, respectively. However, the present study firstly reported a relatively low occurrence rate of 2.17% of IFI in HM inpatients in Southwest China, in contrast to the emerging alarm for high incidence of IFI ranging from 5% to 30% worldwide.[25–27] Given that AML was the most common malignancy in this study and AML patients have been reported more responsive to antifungal agents than those with other leukemia,[28,29] the low IFI incidence might be partially ascribed to malignancy heterogeneity. More importantly, the latest

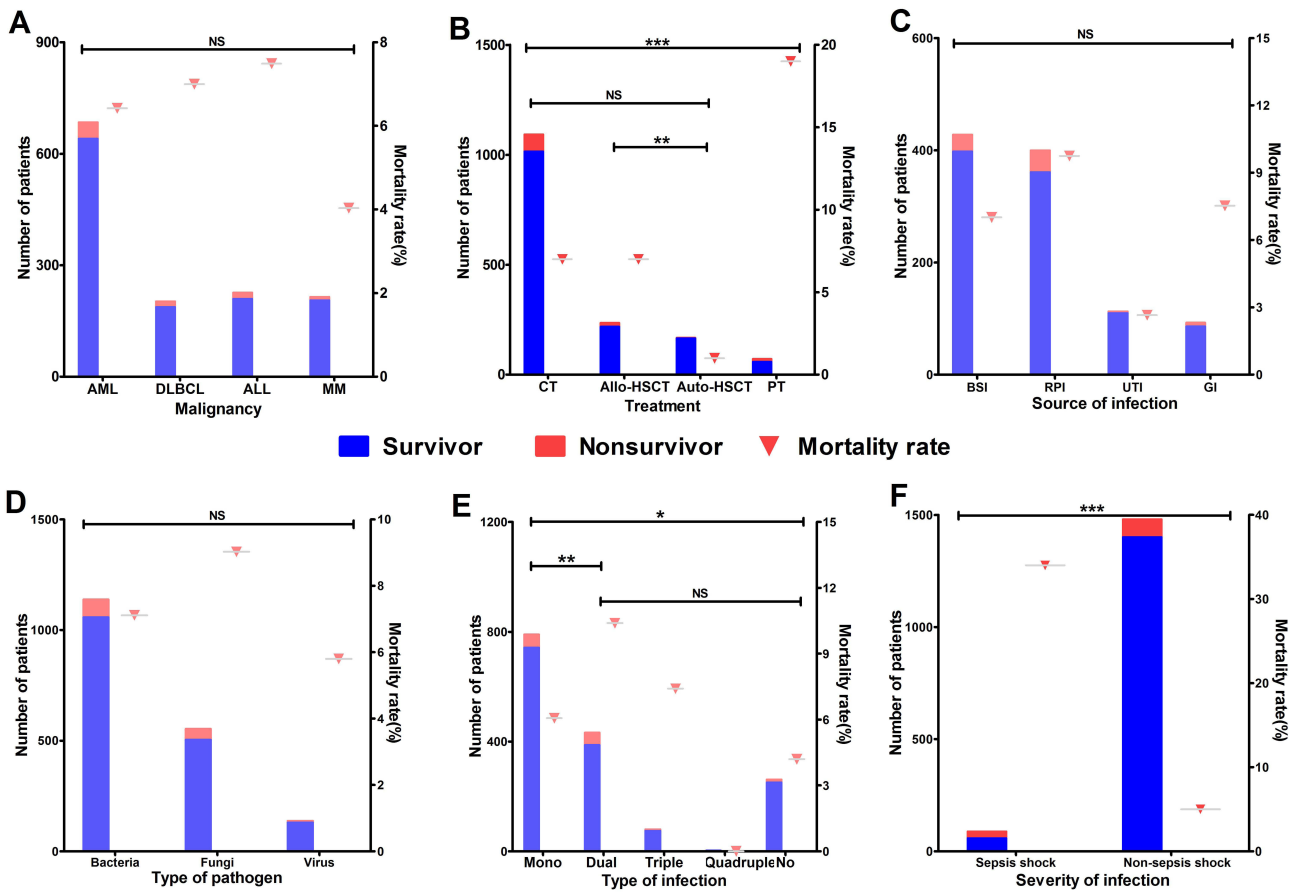


**Figure 4** The in-hospital mortality of HM inpatients with distinct (**A**) types of malignancy, (**B**) treatments, (**C**) source of infection, (**D**) microbial, (**E**) quantities of microbial, and (**F**) severity of infection. Differences between the groups were assessed using Chi-square or Fisher's exact test. Asterisks indicate statistical significance as *P*-values were less than *0.05, **0.01 or ***0.001.

**Abbreviations**: NS, No statistical significance, AML, Acute myeloid leukemia; DLBCL, Diffuse large B-cell lymphoma; ALL, Acute lymphocytic leukemia; MM, Multiple myeloma; HSCT, Hematopoietic stem cell transplantation; Auto-HSCT, Autogeneic hematopoietic stem cell transplantation; Allo-HSCT, Allogeneic hematopoietic stem cell transplantation; PT, Palliative treatment; CT, Chemotherapy; BSI, Bloodstream infections; RPI, Respiratory infections; UTI, Urinary tract infections; GI, Gut infections.

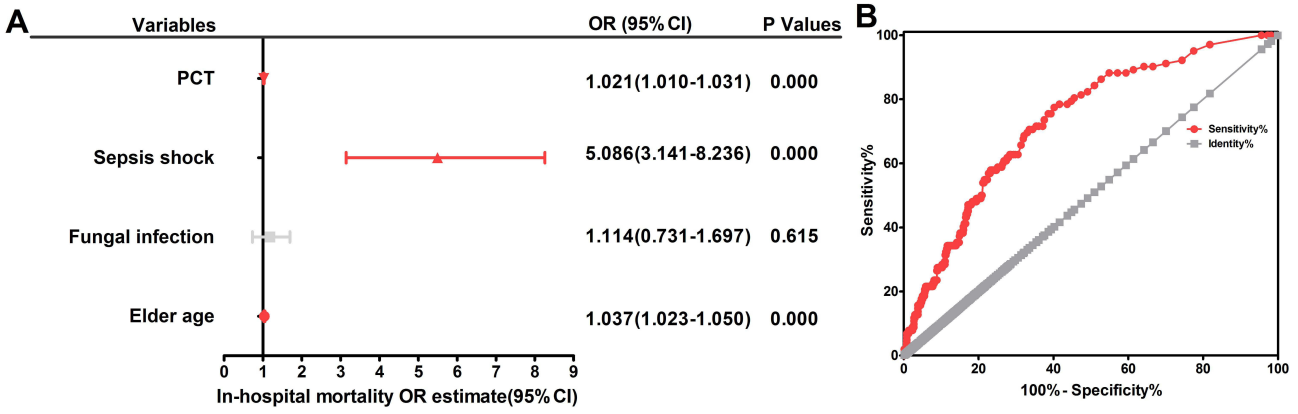


**Figure 5** (**A**) Cox regression analysis of predictors of in-hospital mortality and (**B**) ROC curves of PCT for predicting in-hospital mortality. (**A**) predictors of in-hospital mortality with red color indicate statistical significance.

**Abbreviations**: PCT, Procalcitonin; HSCT, Hematopoietic stem cell transplantation; OR, Odds ratio; CI, Confidence interval.

China Hospital Invasive Fungal Surveillance Net (CHIF-NET) Study has highlighted the geographical heterogeneity of fungal species and Azole susceptibility in IFI.[30] Since *Candida tropicalis* was the most frequent species in this setting and our previous study has reported that more than 90% of *Candida tropicalis* strains were susceptible to Azole agents,[31] it is

assumed that Azole prophylaxis in HM inpatients during curative therapies is effective to prevent and combat IFI, particularly invasive candidemia, and thus results in a low occurrence of IFI in this setting.

Moreover, the low occurrence of IFI and high Azole susceptibility of fungal species may contribute to our relatively low mortality rate of 9.0%, in contrast with those of Spain,[32] Japan,[33] and Southeast Asia,[25] as a majority of IFI deaths have been ascribed to Azole-resistant strains.[34] Furthermore, the association of fungal infection and in-hospital mortality was insignificant in this cohort, which was inconsistent with the result of the NACSELD Cohort.[35] This discrepancy may link to the severity of infection, as a majority of fungal infections in this setting were oral, sinusal, and naso-pharyngeal candidiasis. Another potential explanation is that our study adopted a Cox proportional hazards model to evaluate the potential association between fungal infection and in-hospital mortality. In consideration that long length of hospital stay has been frequently reported as an independent risk factor of fungal infection and in-hospital mortality among HM patients,[13] it is necessary to preclude this co-factor during evaluating the association between them. Since the Cox proportional hazards model has stronger power than logistic regression analysis by adjustment of the length of time,[36] our irrelevance between fungal infection and in-hospital mortality was more convincing.

Of note, this study found that HM inpatients with distinct sources of infection had a comparable in-hospital mortality rate, despite those with respiratory infection seeming to have a higher mortality rate of over 9.0% than those with bloodstream infection or urinary tract infection. This is contradictory to a recent prospective study demonstrating that respiratory infection was more prone to have adverse outcomes than bloodstream infection and urinary tract infection.[37] It was deduced that our result of irrelevance between sources of infection and in-hospital mortality was more convincing for precluding selection bias, as the aforementioned prospective study was limited to carbapenem-resistant *Klebsiella pneumoniae*, the most frequent but hard to treat causative pathogen in hospital-acquired pneumonia. However, it should be noted that multi-drug resistant bacteria has been linked to poor outcomes of patients with HM, especially carbapenem-resistant Gram negative bacteria,[38,39] despite that our study failed to record the antimicrobial susceptibility phenotypes of bacteria strains due to the limited resources.

Surprisingly, a relatively high prevalence of 32.87% of co-infection in this cohort was previously unreported in Southwest China. Systematic reviews have concluded the ubiquity of co-infection and its detrimental effect on clinical outcomes.[40,41] Nevertheless, scarce studies had referred to the quantities of co-infecting pathogens with clinical outcomes. Our findings verified that HM inpatients with dual infection rather than triple or quadruple infection suffered a higher mortality rate than those with mono-infections, but none of those co-infections was associated with early survival or in-hospital mortality of HM inpatients. A plausible interpretation is that co-infections are more likely to occur in severely ill patients with HM.

A high in-hospital mortality rate of 33.71% in HM patients with septic shock was firstly reported in this setting and it was septic shock rather than type of malignancies, treatments, or causative pathogens that determined the outcome of HM patients with infectious complications. These findings were also verified in the Beirut Medical Center[24] and European ICUs,[42] demonstrating a similar early mortality rate of 40% and the independence of early death with type of malignancies or treatments. Although Oeyen et al[43] illustrated that the type of cancer was an important predictor of in-hospital mortality, we insisted that it was the severity of clinical status rather than cancer itself that determines the outcome, as several studies have evidenced similar mortality between hematological malignancies and solid tumors in the intensive care unit.[24,44]

Furthermore, PCT ≥0.24 ng/mL predicted the in-hospital mortality of HM patients with good performance in this setting. Recent data from The University of Texas MD Anderson Cancer Center illustrated that febrile neutropenia patients with PCT ≥0.25 ng/mL were more prone to have 14-day mortality. This is in general accordance with our findings. A similar conclusion had also been reached by Sakshi Yadav[42] and Peipei Liang et al,[45,46] demonstrating PCT as a useful tool for predicting the 30-day mortality of cancer patients with febrile neutropenia or sepsis. However, Uys et al[47] denied the significance of PCT in predicting mortality. This controversy may be ascribed to the heterogeneity in the enrollment criteria of subjects and the definition of outcomes. Since this present study enrolled the current largest cohort of HM patients with infections, not simply those with febrile neutropenia, and was designed in a case-control manner, our finding is more plausible for PCT predictor in favor of beneficial outcomes in this cohort.

Several limitations of our study should not be neglected. Firstly, although it was a ten-year longitudinal study including 1,570 HM patients with infections, its retrospective and single-center nature suggests careful interpretation of these results in other settings. Secondly, despite infection of participants being diagnosed by the consensus of doctors and microbial evidence in this study, there were 16.62% (261/1,570) of participants with suspicious infection, which failed to be evidenced by laboratory microbial testing, and this may bring selective bias. Thirdly, since previous studies have concluded that the disease stage was not related with hospital mortality of HM patients,[14,48] this study did not investigate the association of in-hospital mortality of HM patients with their disease status (new diagnosis, remission, relapse or progression) under infectious background.

## Conclusions

Distinct infection profiles of HM inpatients were previously unreported in Southwest China. The impact of this difference on the outcomes was insignificant and septic shock was positively associated with the 30-day survival and in-hospital mortality, rather than the type of malignancies, treatments, causative pathogens, or quantity of microbial infections. HM inpatients with PCT (≥0.24 ng/mL) and septic shock may have poor outcomes. Timely antimicrobial prophylaxis and treatment of infection and early recognition of septic shock were advocated.

## Data Sharing Statement

All the data of this article are available from the corresponding author upon reasonable request.

## Acknowledgments

The authors would like to thank all their colleagues for their participation in the testings for laboratory evidence of infection.

## Author Contributions

All authors contributed to the design of this study and made significant contributions to data collection, drafting of this manuscript, interpretation of data, and revision of the manuscript, gave the final approval of the submission version for publication, agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

## Funding

This work is sponsored by National Natural Science Foundation of China (82002255), Natural Science Foundation of Chongqing, China (cstc2021jcyj-msxmX0217), Chongqing medical scientific research project (Joint project of Chongqing Health Commission and Science and Technology Bureau, 2022QNXM002) and CQMU Program for Youth Innovation in Future Medicine (W0104).

## Disclosure

None of the authors have conflicts of interest relevant to this manuscript to declare.

## References

1. Atkins S, He F. Chemotherapy and beyond: infections in the era of old and new treatments for hematologic malignancies. *Infect Dis Clin North Am*. 2019;33(2):289–309. doi:10.1016/j.idc.2019.01.001
2. Tau N, Shargian-Alon L, Reich S, et al. Reporting infections in clinical trials of patients with haematological malignancies. *Clin Microbiol Infect*. 2019;25(12):1494–1500. doi:10.1016/j.cmi.2019.04.029
3. Schulz E, Grumaz S, Hatzl S, et al. Pathogen detection by metagenomic next-generation sequencing during neutropenic fever in patients with hematological malignancies. *Open Forum Infect Dis*. 2022;9(8):ofac393. doi:10.1093/ofid/ofac393
4. Takeshita K, Ishiwada N, Takeuchi N, et al. Immunogenicity and safety of routine 13-valent pneumococcal conjugate vaccination outside recommended age range in patients with hematological malignancies and solid tumors. *Vaccine*. 2022;40(9):1238–1245. doi:10.1016/j.vaccine.2022.01.056
5. Kiderlen TR, Trostdorf K, Delmastro N, Salomon A, de Wit M, Reinwald M. Herpes zoster vaccination rates in hematological and oncological patients-stock taking 2 years after market approval. *Healthcare*. 2022;10(8):1524. doi:10.3390/healthcare10081524

6. Beyar-Katz O, Bitterman R, Zuckerman T, Ofran Y, Yahav D, Paul M. Anti-herpesvirus prophylaxis, pre-emptive treatment or no treatment in adults undergoing allogeneic transplant for haematological disease: systematic review and meta-analysis. *Clin Microbiol Infect*. 2020;26(2):189–198. doi:10.1016/j.cmi.2019.09.003
7. Lionakis MS, Lewis RE, Kontoyiannis DP. Breakthrough invasive mold infections in the hematology patient: current concepts and future directions. *Clin Infect Dis*. 2018;67(10):1621–1630. doi:10.1093/cid/ciy473
8. Christopeit M, Schmidt-Hieber M, Sprute R, et al. Prophylaxis, diagnosis and therapy of infections in patients undergoing high-dose chemotherapy and autologous haematopoietic stem cell transplantation. 2020 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Ann Hematol*. 2021;100(2):321–336. doi:10.1007/s00277-020-04297-8
9. Hardak E, Avivi I, Berkun L, et al. Polymicrobial pulmonary infection in patients with hematological malignancies: prevalence, co-pathogens, course and outcome. *Infection*. 2016;44(4):491–497. doi:10.1007/s15010-016-0873-3
10. Danion F, Duval C, Severac F, et al. Factors associated with coinfections in invasive aspergillosis: a retrospective cohort study. *Clin Microbiol Infect*. 2021;27(11):1644–1651. doi:10.1016/j.cmi.2021.02.021
11. Huang LW, Wong SW, Andreadis C, Olin RL. Updates on hematologic malignancies in the older adult: focus on acute myeloid leukemia, chronic lymphocytic leukemia, and multiple myeloma. *Curr Oncol Rep*. 2019;21(4):35. doi:10.1007/s11912-019-0778-2
12. Amanati A, Sajedianfard S, Khajeh S, et al. Bloodstream infections in adult patients with malignancy, epidemiology, microbiology, and risk factors associated with mortality and multi-drug resistance. *BMC Infect Dis*. 2021;21(1):636. doi:10.1186/s12879-021-06243-z
13. Chen XC, Xu J, Wu DP. Clinical characteristics and implications of mixed candida/bacterial bloodstream infections in patients with hematological diseases. *Eur J Clin Microbiol Infect Dis*. 2020;39(8):1445–1452. doi:10.1007/s10096-020-03863-2
14. Manjappachar NK, Cuenca JA, Ramirez CM, et al. Outcomes and predictors of 28-day mortality in patients with hematologic malignancies and septic shock defined by sepsis-3 criteria. *J Natl Compr Canc Netw*. 2022;20(1):45–53. doi:10.6004/jnccn.2021.7046
15. Sung L, Lange BJ, Gerbing RB, Alonzo TA, Feusner J. Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia. *Blood*. 2007;110(10):3532–3539. doi:10.1182/blood-2007-05-091942
16. Liu Y, Ling L, Wong SH, et al. Outcomes of respiratory viral-bacterial co-infection in adult hospitalized patients. *EClinicalMedicine*. 2021;37:100955. doi:10.1016/j.eclinm.2021.100955
17. Torres JP, Labrana Y, Ibanez C, et al. Frequency and clinical outcome of respiratory viral infections and mixed viral-bacterial infections in children with cancer, fever and neutropenia. *Pediatr Infect Dis J*. 2012;31(9):889–893. doi:10.1097/INF.0b013e31825c4b7e
18. Liu YN, Zhang YF, Xu Q, et al. Infection and co-infection patterns of community-acquired pneumonia in patients of different ages in China from 2009 to 2020: a national surveillance study. *Lancet Microb*. 2023;4(5):e330–e339. doi:10.1016/S2666-5247(23)00031-9
19. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315(8):801–810. doi:10.1001/jama.2016.0287
20. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49(1):1–45. doi:10.1086/599376
21. Hage CA, Carmona EM, Epelbaum O, et al. Microbiological laboratory testing in the diagnosis of fungal infections in pulmonary and critical care practice. an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2019;200(5):535–550. doi:10.1164/rccm.201906-1185ST
22. Naranjo RL. A pretest for choosing between logrank and Wilcoxon tests in the two-sample problem. *METRON Int J Stat*. 2010;68:111–125.
23. David O, Fruchtman Y, Sergienko R, Kapelushnik J, Leibovitz E. The Infectious and noninfectious etiology, clinical picture and outcome of neutropenia in immunocompetent hospitalized children. *Pediatr Infect Dis J*. 2018;37(6):570–575. doi:10.1097/INF.0000000000001893
24. Bou Chebl R, Safa R, Sabra M, et al. Sepsis in patients with haematological versus solid cancer: a retrospective cohort study. *BMJ Open*. 2021;11(2):e038349. doi:10.1136/bmjopen-2020-038349
25. Chen CY, Sheng WH, Tien FM, et al. Clinical characteristics and treatment outcomes of pulmonary invasive fungal infection among adult patients with hematological malignancy in a medical centre in Taiwan, 2008–2013. *J Microbiol Immunol Infect*. 2020;53(1):106–114. doi:10.1016/j.jmii.2018.01.002
26. On S, Rath CG, Lan M, et al. Characterisation of infections in patients with acute myeloid leukaemia receiving venetoclax and a hypomethylating agent. *Br J Haematol*. 2022;197(1):63–70. doi:10.1111/bjh.18051
27. Souza L, Nouer SA, Morales H, et al. Epidemiology of invasive fungal disease in haematologic patients. *Mycoses*. 2021;64(3):252–256. doi:10.1111/myc.13205
28. Oh SM, Byun JM, Chang E, et al. Incidence of invasive fungal infection in acute lymphoblastic and acute myelogenous leukemia in the era of antimold prophylaxis. *Sci Rep*. 2021;11(1):22160. doi:10.1038/s41598-021-01716-2
29. Maertens JA, Girmenia C, Bruggemann RJ, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. *J Antimicrob Chemother*. 2018;73(12):3221–3230. doi:10.1093/jac/dky286
30. Xiao M, Sun ZY, Kang M, et al. Five-year national surveillance of invasive candidiasis: species distribution and azole susceptibility from the China Hospital Invasive Fungal Surveillance Net (CHIF-NET) Study. *J Clin Microbiol*. 2018;56(7):e00577–00518. doi:10.1128/JCM.00577-18
31. Pu S, Niu S, Zhang C, et al. Epidemiology, antifungal susceptibilities, and risk factors for invasive candidiasis from 2011 to 2013 in a teaching hospital in southwest China. *J Microbiol Immunol Infect*. 2017;50(1):97–103. doi:10.1016/j.jmii.2015.01.005
32. Puig-Asensio M, Ruiz-Camps I, Fernandez-Ruiz M, et al. Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain. *Clin Microbiol Infect*. 2015;21(5):491.e1–10. doi:10.1016/j.cmi.2014.12.027
33. Kobayashi R, Hori D, Sano H, Suzuki D, Kishimoto K, Kobayashi K. Risk factors for invasive fungal infection in children and adolescents with hematologic and malignant diseases: a 10-year analysis in a single institute in Japan. *Pediatr Infect Dis J*. 2018;37(12):1282–1285. doi:10.1097/INF.0000000000002010
34. Badali H, Canete-Gibas C, McCarthy D, et al. Species distribution and antifungal susceptibilities of aspergillus section fumigati isolates in clinical samples from the United States. *J Clin Microbiol*. 2022;60(5):e0028022. doi:10.1128/jcm.00280-22
35. Bajaj JS, Reddy RK, Tandon P, et al. Prediction of fungal infection development and their impact on survival using the NACSELD Cohort. *Am J Gastroenterol*. 2018;113(4):556–563. doi:10.1038/ajg.2017.471

36. van der Net JB, Janssens AC, Eijkemans MJ, Kastelein JJ, Sijbrands EJ, Steyerberg EW. Cox proportional hazards models have more statistical power than logistic regression models in cross-sectional genetic association studies. *Eur J Hum Genet*. 2008;16(9):1111–1116. doi:10.1038/ejhg.2008.59
37. Hauck C, Cober E, Richter SS, et al. Spectrum of excess mortality due to carbapenem-resistant Klebsiella pneumoniae infections. *Clin Microbiol Infect*. 2016;22(6):513–519. doi:10.1016/j.cmi.2016.01.023
38. Di Domenico EG, Marchesi F, Cavallo I, et al. The impact of bacterial biofilms on end-organ disease and mortality in patients with hematologic malignancies developing a bloodstream infection. *Microbiol Spectr*. 2021;9(1):e0055021. doi:10.1128/Spectrum.00550-21
39. Lu L, Xu C, Tang Y, et al. The threat of carbapenem-resistant gram-negative bacteria in patients with hematological malignancies: unignorable respiratory non-fermentative bacteria-derived bloodstream infections. *Infect Drug Resist*. 2022;15:2901–2914. doi:10.2147/IDR.S359833
40. McArdle AJ, Turkova A, Cunnington AJ. When do co-infections matter? *Curr Opin Infect Dis*. 2018;31(3):209–215. doi:10.1097/QCO.0000000000000447
41. Gorsich EE, Etienne RS, Medlock J, et al. Opposite outcomes of coinfection at individual and population scales. *Proc Natl Acad Sci USA*. 2018;115(29):7545–7550. doi:10.1073/pnas.1801095115
42. Lemiale V, Pons S, Mirouse A, et al. Sepsis and septic shock in patients with malignancies: a groupe de recherche respiratoire en reanimation onco-hematologique study. *Crit Care Med*. 2020;48(6):822–829. doi:10.1097/CCM.0000000000004322
43. Oeyen SG, Benoit DD, Annemans L, et al. Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies: a single center study. *Intensive Care Med*. 2013;39(5):889–898. doi:10.1007/s00134-012-2791-x
44. Xiang MJ, Chen GL. Impact of cancer on mortality rates in patients with sepsis: a meta-analysis and meta-regression of current studies. *World J Clin Cases*. 2022;10(21):7386–7396. doi:10.12998/wjcc.v10.i21.7386
45. Yadav S, Mathew R, Sahu AK, et al. Prognostic value of serum procalcitonin levels in patients with febrile neutropenia presenting to the emergency department. *J Emerg Med*. 2021;60(5):641–647. doi:10.1016/j.jemermed.2020.12.010
46. Liang P, Yu F. Value of CRP, PCT, and NLR in prediction of severity and prognosis of patients with bloodstream infections and sepsis. *Front Surg*. 2022;9:857218. doi:10.3389/fsurg.2022.857218
47. Uys A, Rapoport BL, Fickl H, Meyer PW, Anderson R. Prediction of outcome in cancer patients with febrile neutropenia: comparison of the multinational association of supportive care in cancer risk-index score with procalcitonin, C-reactive protein, serum amyloid A, and interleukins-1beta, −6, −8 and −10. *Eur J Cancer Care*. 2007;16(6):475–483. doi:10.1111/j.1365-2354.2007.00780.x
48. Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care*. 2004;8(5):R291–298. doi:10.1186/cc2893



**Infection and Drug Resistance** Dovepress

## Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

**Submit your manuscript here:** https://www.dovepress.com/infection-and-drug-resistance-journal