Assessment of infection in newly diagnosed multiple myeloma patients: Risk factors and main characteristics

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Abstract

Background: Infection is a leading cause of morbidity and death in patients with multiple myeloma (MM). The increased susceptibility to infection is complicated and multifactorial. However, none of the studies had assessed the risk of infection in MM patients who didn't receive the antitumor treatment. For the first time, this study aimed to provide ideas for the assessment, prevention and treatment of infection in newly diagnosed MM patients without antitumor therapy. Methods: Retrospectively, the data from electronic medical records for 161 cases of hospitalized patients with multiple myeloma were analyzed, during May 2013 to December 2018. Independent risk factors of infection in multiple myeloma were determined by univariate and multivariate analysis. Results: Newly diagnosed patients with MM were highly susceptible to viruses (43.9%), especially the EBV (24.4%) and HBV (17.1%). More advanced stage (ISS-Ⅲ stag, P=0.040), more severe anemia (Hb<90 g/L, P=0.044) and the elevation of CRP (>10 mg/L, P=0.006) were the independent risk factors of infection. Moreover, infections represented a major threat to patients with newly diagnosed MM (P = 0.033), and the existence of risk factors for infection was significantly related to poor prognosis (P = 0.011), especially the ISS-Ⅲ stage (P=0.008) and lower hemoglobin level (P=0.039). Conclusions: MM patients without antitumor therapy are highly susceptible to viruses. Advanced ISS stage, more severe anemia and the elevation of CRP were identified as independent risk factors of infection, which also have a strong impact on the prognosis. Our results suggest that the viral infection should be taken into account if antibacterial drugs are not effective, and the prevention of infection and improvement of prognosis should be paid more attention to in the newly diagnosed patents with more advanced stage and more severe anemia.

1. Introduction

Multiple myeloma (MM) is a malignant proliferating disease of plasma cells characterized by bone pain, anemia, renal insufficiency and hypercalcemia. Clonal plasma cells in bone marrow proliferate abnormally and secrete monoclonal immunoglobulin or M protein, resulting in damage of related organs or tissues. MM as the second most common hematologic neoplasm accounts for approximately 2% of cancer-related mortalities.

Infection is a significant cause of morbidity and a principal cause of death in patients with MM [1-5], mainly occur in the elderly [6]. In a recent research [7], compared with matched controls, the risk of developing a bacterial infection increased 7-fold, and for viral infections 10-fold in MM patients. Augustson *et al*. [8] observed that almost 50% of early deaths (< 6 months) were due to infections, in the study of over 3000 newly diagnosed MM patients. The increased susceptibility to infection in MM patients is complicated and multifactorial, probably due to the disease-related immune deficits on innate or adaptive immune system, including hypogammaglobulinemia [9-11], numerical and functional abnormalities of dendritic cells [12], T cells [13] and natural killer cells [14], and renal function impairment [9].

Except for the inherent immune deficiency, some surveys have described a changing spectrum of infections in MM, perhaps related to the more innovative treatment approach of recent years, indicating that the novel agents may increase the risk of infections in patients with MM [15-18], however controversies still exist. Historically, these infections were most prevailing in untreated patients or early induction therapy [19-21]. Cesana *et al*. [22] proved that the incidence of infection in early period (≤ 4 months) of treatment was significantly higher than later period, and previously untreated multiple myeloma was significantly correlated with bacterial infection risk. Therefore, doing research into the infection of newly diagnosed patients with MM and preventing the death from infections are paramount. However, none of the studies had assessed the risk of infection in newly diagnosed MM patients who didn't receive the antitumor treatment. For the first time, we included the newly diagnosed MM patients at the first visit, and none of them was treated previously.

In this study, we comprehensively analyzed a variety of clinical and laboratory parameters associated with infectious complications to describe the characteristics and identify the risk factors of infection in newly diagnosed MM patients. At the same time, we explored the impact of risk factors on survival. The ultimate purpose is to help with developing strategies for the assessment, prevention and treatment of infection, so as to improve the prognosis of the MM patients without antitumor therapy.

2. Methods

2.1 Patients

We took retrospective data from electronic medical records for 161 cases of newly diagnosed patients with multiple myeloma, who were first hospitalized in our department from May 2013 to December 2018. None of the patients had received treatment previously. The diagnosis of MM was based on International Myeloma Working Group (IMWG) criteria [23]. And this study was approved by the ethics committees/institutional review boards.

For all included cases, we obtained information on patient demographics, such as age, sex and Eastern Cooperative Oncology Group (ECOG) score. The infection-related datum included microbial species, infection sites, neutrophil, lymphocytes, C-reactive protein (CRP), invasive operation and catheters. Besides, the indicators related to MM disease included RBC, hemoglobin, albumin, globulin, serum creatinine, serum calcium, β2-microglobulin (β2-MG), lactate dehydrogenase (LDH) and clinical features (mainly including Immunophenotype, Durie-Salmon stage, International Staging System stage, bone destruction, complications and survival time). Patients were followed until 31 December 2018 or death, whichever came first.

2.2 Measurements and Definitions

The criteria for infection used in our study were the existence of a pathogen, imaging evidence of infection combined with concomitant clinical symptoms, such as non-pharmacological rise in body temperature (≥37 °C), cough with sputum, painful urination and so on. Bacteria and fungus were

identified by morphological, biochemical and serological reactions, after isolation, purification and cultivation. The diagnosis of virus was using polymerase chain reaction (PCR) technology to amplify the DNA or RNA, such as Epstein-Barr virus (EBV), Hepatitis B virus (HBV) and Hepatitis C virus (HCV). Meanwhile, indirect immunofluorescence assay and chemiluminescence microparticle immunoassay were used to detect the IgM antibodies against respiratory syncytial virus (RSV), adenovirus, influenza virus, cytomegalovirus (CMV) and so on.

The cases were grouped as Microbiologically-defined infections (MDI), when the microbiological assay of blood or secretion samples from any site indicated pathogen infections. Simultaneously, the cases were grouped as Clinically-defined infection (CDI), when the results of microbiological assay were negative, while the imaging evidence and clinical symptoms of infection exist. The MDI and CDI constituted the group with infections, the other cases without the proof of infection were classified as the group without infections.

2.3 Statistical Analyses

All analyses were performed using SPSS 21.0. Comparisons between groups for categorical variables were performed using chi-square test with Yates' correction or Fisher's exact test when appropriate. Univariate analysis of infection rates was also performed by chi-square test to screen the influencing factors of infection. The factors with $P < 0.05$ were selected and included in the multivariate analysis, which was performed using binary logistic regression model (Forward LR). From the multivariate analysis, potential confounding factors and multicollinearity were evaluated, and factors closely associated with other significant factors were excluded. $P < 0.05$ was considered to be statistically significant. The survival curves were calculated using the Kaplan-Meier method and were compared using the log-rank test. A P value of < 0.05 was defined as statistically significant.

3. Results

3.1 Patients' characteristics

Overall, we analyzed 161 patients for the first hospitalization with newly diagnosed multiple myeloma (94 males and 67 females). The average age was 64 years (range of 41-85) and 67.3% of patients were ≥60 years. 100 patients had an ECOG score of 0 or 1, while 61 patients had a score ≥2. A total of 70 patients (43.5%) had MM of the IgG type, 30.4% of IgA type and 19.9% of light-chain type. With regard to the Durie-Salmon (DS) stag, 10 patients were stage I, 26 were stage II, and 122 were stage III. With regard to the International Staging System (ISS) stage, 10 patients were stage I, 46 were stage II, and 101 were stage III.

Of all patients, 99 (61.5%) had bone destruction, 138 (85.7%) underwent invasive operation, 42 (26.1%) were placed catheter, and 106 (65.8%) were accompanied by complication. Infections were found in 126

of 161 (78.3%) hospitalized patients. Of these, 31 (24.6%) were microbiologically defined (MDI), and 95 (75.4%) were clinically defined (CDI). Besides, 35 patients were uninfected.

3.2Distribution of the infection sites

Add up to 173 infection sites were found in 126 patients with infection. The most common site of infection was the respiratory system in 112 cases (64.7%), followed by the immune system (21 cases, 12.1%), digestive system (19 cases, 11.0%), urinary system (12 cases, 6.9%) and circulatory system (4 cases, 2.3%). The others included 3 cases of alveolar osteitis and 2 cases of unknown site. In 43/126 cases (34.1%), more than 1 site of infections was found. Furthermore, CDI accounted for a higher proportion in respiratory infections (P=0.044). And MDI mainly appeared in the infection of urinary, digestive and circulatory systems (P=0.001, P=0.027, P=0.046, respectively). The distribution of infected sites is summarized in **Figure 1**.

3.3 Distribution of the pathogens

41 pathogens of the infections were identified in the research. Unexpectedly, virus (43.9%) were the main cause of infection. Followed by bacteria (36.6%) including 22.0% gram-negative bacteria and 14.6% gram-positive bacteria. Besides, fungus accounted for 19.5%.

It's worth mentioning that the constituent ratios of EBV (24.4%) was highest in all of the pathogenic microorganisms. After that, the HBV (17.1%) was in second place, the Candida albicans (12.2%) and Escherichia coli (12.2%) ranked third. Furthermore, 4 cases of herpes zoster infection were clinically diagnosed but without the microbiological examination for herpes zoster virus (HZV). Therefore, it was not included in the list of pathogens. The constituent ratios of causative agents are shown in **Table 1**.

The vast majority of patients in microbiologically defined infections were infected with only one pathogen (25/31 cases). Fewer than a quarter of microbiologically-defined patients suffered more than one pathogen attacks. Among them, 3 cases of infections with two pathogens, and 2 cases with three, 1 case with four.

3.4 Influencing factors of infection

According to the univariate analysis (**Table 2**), the factors associated with more frequent infections were poor performance status (ECOG>2, P=0.038), more advanced stage (Durie-Salmon stage Ⅲ, P=0.011; ISS stag Ⅲ, P=0.005), more severe anemia (Hb<90 g/L, P=0.014), the elevation of CRP (>10 mg/L, P=0.007) and the presence of catheter (P=0.026). Nevertheless, neutropenia (ANC<1.5×10^9 vs. ≥1.5×10^9, P=1.000) and lymphocytopenia (ALC<1.0×10^9 vs. ≥1.0×10^9, P=0.055), did not display significant difference.

Multivariate logistic regression analysis (**Table 3**) demonstrated that more advanced stage (ISS stag Ⅲ, P=0.040), more severe anemia (Hb<90 g/L, P=0.044) and the elevation of CRP (>10 mg/L, P=0.006) were the independent risk factors of infections. And there was no collinearity among the factors (VIF < 2, tolerance > 0.85, respectively).

The probability of infection was 38.1% in the absence of risk factors, 80.4% with 1 risk factor, 82.1% with 2 risk factors, 96.3% with 3 risk factors (P<0.001, **Figure 2**). Visibly, the occurrence of independent risk factors significantly increased the infection rate (risk factors Yes vs. No, P < 0.001).

3.5 Outcome analysis

We counted and analyzed the infection of the first hospitalization in newly diagnosed patients with MM to draw the Kaplan Meier survival curve (**Figure 3A**). The infected group showed a significantly shorter median OS compared with the uninfected group (29 months vs. not reached, P = 0.033). In our study, only one death occurred in the newly diagnosed patients without risk factors, besides we found that the median OS of the patients with independent risk factors was significantly shorter than that without independent risk factors (29 months vs. not reached, P = 0.011) (**Figure 3B**). Through further analysis, among the risk factors, more advanced stage (ISS stag) and more severe anemia (Hb<90 g/L) were related to shorter survival time. Patients with ISS- stage had an obviously shorter median OS than that with ISS stage- (24 months vs. 35 months, P = 0.008) (**Figure 3C**). In addition, the median OS of patients with low serum hemoglobin level (Hb<90 g/L) was apparently shorter than that with Hb≥90 g/L (24 months vs. not reached, P = 0.039) (**Figure 3D**).

4. Discussion

Patients with MM suffered immune deficiency in varying degrees, which increased the risk of severe infections [3, 4, 24]. Similar to the previous studies [6, 8, 19, 22, 25-27], infection was common in newly diagnosed patients with MM and appeared to be the initial manifestation and the leading cause of death, mainly occurred in the elderly. In order to provide ideas for the assessment, prevention and treatment of infection in newly diagnosed MM patients without the antitumor therapy, we explored the characteristics and risk factors of infection in 161 patients who were first hospitalized in our department.

According to our cases, infections occurred in 78.3% cases of newly diagnosed patients with MM in our ward from May 2013 to December 2018. Respiratory infections were in the majority (64.7%), which was in concordance with the existing data [19, 25, 26, 28]. Urinary, digestive and circulatory systems were more likely to cause the microbial infection (P=0.001, P=0.027, P=0.046, respectively), which may be related to the placement of catheters. Additionally, we found viral (43.9%) and bacterial (36.6%) infections represent a major threat to MM patients, as reported by Blimark *et al*. [7]. For the first time, the viruses overtook bacteria and occupied the first place, meanwhile, EBV and HBV accounted for the major proportion in our study, which was different from the known research [28-31] (considered that gram-negative bacteria such as Escherichia coli and Pseudomonas aeruginosa are the leading pathogens). However, whether there is an upward trend in the infection rate of the virus remains to be verified.

Patients with multiple myeloma are more susceptible to the virus [32]. Blimark *et al.* [7] showed that the risk of developing viral infection in patients with MM was 10 times higher compared with matched

controls. Through molecular analysis, a recent study [33] displayed a significant EBV DNA in malignant plasma cell disorders, especially in MM and MGUS (monoclonal gammopathy of undetermined significance) patients. Bosseboeuf *et al*. [34] demonstrated that EBV was the most frequent target of purified monoclonal IgG which produced by patients with MGUS or MM. They considered that chronic stimulation by infectious Ag may promote MGUS and MM. It can be concluded that EBV has been associated with MM. An early study [35] confirmed that HBV was lymphotrophic, and was able to infect and replicate in human lymphocytes and monocytes. A study in Japan [36] reported that the rate of HBV infection in patients with MM was 3.2%, higher than that in the group of healthy subjects (1.2%). Huang et al. [37] found that the patients with MM had significantly higher HBV carrier rate than acute leukemia, and patients with MM who were HBV carriers were at significantly higher risk of having hepatic injury than non-carriers. Coinciding with the views of early researchers, we believed that viruses play an important role in patients with MM, especially the EBV and HBV in our study. Therefore, the prevention and treatment of the virus in newly diagnosed patients with MM is essential. If an underlying chronic infection was cleared up early enough in disease progression, it could perhaps offer the possibility to prevent MGUS transition to SM and MM in the first place [34]. In addition, we agree with the point that newly diagnosed patients with MM should be screened for serum hepatitis B viral markers universally in HBV endemic areas [37].

In our research, according to the univariate and multivariate analysis, we demonstrated that advanced ISS stage (ISS stage Ⅲ), more severe anemia (Hb<90 g/L) and the elevation of CRP (>10 mg/L) were identified as independent determinants of infection patients with MM. Meanwhile, poor performance status (ECOG>2), advanced DS stage (DS Ⅲ) and the presence of catheter were the influencing factors of infection. Nevertheless, ANC and ALC did not display significant difference. Compared with the previous report in recent years, Huang *et al*. [19] showed that advanced ISS stage (ISS stage Ⅲ) and poor ECOG performance status (ECOG>2) were the independent risk factors of blood stream infections (BSI) in patients with newly diagnosed MM, and more severe anemia (Hb<100 g/L) and worse renal function (Cr≥177 μmol/L) were influencing factors associated with BSI. In addition, ALC showed no significant difference. However, they did not include DS stag, ANC, CRP and catheter in univariate and multivariate analysis, blood stream was the only discussed infection site, and patients received antitumor therapy, which may be the cause for the difference in risk factors of the final model between our researches.

The ISS stage is a widely accepted staging system based on serum levels of albumin and β2-MG [38]. Serum albumin level is inversely correlated with healthy dietary and has been recognized as a sign of rapid tumor growth [39]. In addition, serum β2-MG level is elevated in patients with MM due to renal insufficiency as well as tumor burden. In an unselected cohort, Caravita *et al*. [40] reported that only ISS resulted as risk factor affecting severe infection development. Isoda et al. [41] indicated that advanced ISS stage was an independent risk factor associated with severe (grade C 3) bacterial infection in MM patients. A large number of studies [19, 28, 29] have shown that the advanced ISS stage was an important risk factor of infection in MM patients. In agreement with previous reports, advanced ISS stage appeared to be associated with a higher incidence of infection in our cases as well. In consequence,

similarly we hold the opinion that the patients with ISS-Ⅲ stage, mostly morbid patients with high disease activity, not only have poorer prognosis, but also are susceptible to serious infection complications [41].

The decrease of hemoglobin content, on the one hand, reduces the concentration of respiratory enzyme, mitochondrial oxidase and myoglobin, thus resulted in the deficiency in oxygen supply, decrease of aerobic metabolism and accumulation of lactic acid, on the other hand, affects the immune response and phagocytosis , which in turn leads to the depression of immune functions and disturbances of immune regulation, subsequently increases the risk of infection [42]. It has been found that anemia is a risk factor for accompanying infection in patients with MM, Dumontet *et al*. [43] included hemoglobin in the predictive model of first treatment-emergent (TE) grade ≥ 3 infection in the first 4 months in patients with MM, TE infections were defined as infections that occur or worsen on or after the first dose of any drug and within 28 days after discontinuation of treatment. Similar to early research, lower hemoglobin level also showed a significant correlation with infection in our study, although the patients were not received treatment previously. Therefore, according to European Myeloma Network [44], we consider that patients with persistent symptomatic anemia (hemoglobin <10g/dL) without other cause may initiate treatment with erythropoietic-stimulating agents.

CRP is an acute phase reaction protein (APRP) synthesized by liver cells in response to inflammatory stimuli such as microbial invasion or tissue damage. CRP increases within the first few hours of inflammation and peaks at 48 hours, which is not affected by radiotherapy, chemotherapy or corticosteroid therapy. Rintala *et al*. [45] demonstrated that CRP was a reliable and readily available method to differentiate between bacterial infections and other causes of fever in patients with malignant hematological diseases. What's more, Apewokin *et al*. [46] concluded that the elevated CRP in patients with hematological malignancies could be used as a sensitive screening index for viral infection. In our research, the elevation of CRP was observably related to the risk of infections, and 12 (57.1%) patients with viral infection were accompanied with the elevated CRP, while the rate of increased CRP was 38.6% in patients without viral. So, for severely infected patients with elevated CRP, using antibacterial drugs is not effective, the viral infection should be taken into account.

Numerous previous studies have suggested that neutropenia is a risk factor for infection with MM. High-dose alkylating agents and new drugs can lead to myelosuppression and agranulocytosis, especially in combination [47]. In this study, absolute neutrophil counts (ANC) were all pre-treatment data, 80.1% (100/126) of infected patients were in a normal ANC, and neutropenia accounted for only 11.9% (15/126). Although the occurrence of neutropenia may also due to the disease itself, but it was not reflected in this study, possibly because the remaining myeloid progenitor cells of MM patients still balanced the production and consumption of neutrophil, or the stored mature neutrophil in bone marrow still replenished for the circulating. Moreover, the hematopoietic function was suppressed in patients with MM, and neutrophilia was not necessarily observed during infection. Only 8.7% (11/126) of the patients had neutrophilia in our analysis. As a result, for the newly diagnosed MM patients, the decrease or increase of ANC can't be used as an indicator of infection. The absolute lymphocyte count (ALC) as a marker of host immunity has been widely studied in a variety of malignancies. Although its role on

infections in newly diagnosed MM patients remains indeterminate, the significance on infection risk and survival has been associated with MM during bortezomib treatment [30, 48]. However, ALC did not show any remarkable difference in infections in this research, which may attribute to the fact that patients were not accepted previous treatment.

Newly diagnosed patients with MM have variable survival, ranging from a few days to more than a decade [49, 50]. A large number of studies [1, 2, 7, 8, 27, 30] confirm that infections represent a major threat to patients with MM. A single institution study [27] pointed out that infections contributed most to the early mortality. Caravita*, et al.* [40] attested that the overall survival (OS) of MM patients with infections was significantly shorter compared to that without infections. The same conclusion was reached in our study of newly diagnosed MM patients with infection compared with that without infection (P=0.033). And the median OS of patients with independent risk factors was significantly shorter than that without independent risk factors (P=0.011), among the risk factors, mainly more advanced stage (ISS stag , P=0.008) and more severe anemia (Hb<90 g/L, P=0.039) were significantly associated with the poor prognosis. It can be seen that infection is a significant cause of death in patients with MM, and the existence of independent risk factors of infection seriously affects the prognosis of newly diagnosed MM patients, especially the ISS- stage and the lower hemoglobin level.

There are several limitations of our research. Firstly, the retrospective designed study may have selection biases of patients, and the number of participants is limited. Besides, the performance of interphase fluorescence in situ hybridization (iFISH) in MM patients is not common due to various reasons, such as the expensive price, resulting in a serious lack of information on cytogenetic, so the data of r-ISS stage is not analyzed in our study. However, considering the broadscale clinical application, ISS stage may be of a higher practical value in predicting infection at present. On account of the more important role in evaluating the prognosis of patients with MM, R-ISS also need to be included in the analysis with the popularization of cytogenetic detection technology.

5. Conclusions

Newly diagnosed patients with MM are highly susceptible to viruses, especially Epstein-Barr virus and hepatitis B virus. Advanced ISS stage (ISS stage), more severe anemia (Hb<90 g/L) and the elevation of CRP (>10 mg/L) were identified as independent risk factors of infection. Furthermore, infections represented a major threat to patients with newly diagnosed MM, and the existence of risk factors of infection had a strong impact on the prognosis, especially the ISS- stage and the lower hemoglobin level.

Abbreviations

MM: Multiple Myeloma; EBV: Epstein-Barr virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; RSV: Respiratory Syncytial virus; CMV: Cytomegalovirus; MDI: Microbiologically-defined infections; CDI:

Clinically-defined infection; DS: Durie-Salmon; ISS: International Staging System; ECOG: Eastern Cooperative Oncology Group; RBC: Red Blood Cell; ANC: Absolute Neutrophil Count; ALC: Absolute Lymphocyte Count; CRP: C-reactive protein; β2-MG: β2-microglobulin; LDH: Lactate Dehydrogenase; OS: Overall Survival; MGUS: Monoclonal Gammopathy of Undetermined Significance

Declarations

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Authors' contributions

Chenyao Lin collected, analyzed and interpreted data, and wrote manuscript. Fuling Zhou, Changxin Shen proposed and designed the study. All other authors collected clinical data and provided important insights. All authors proofread the manuscript and agreed on the data presented.

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The research study was approved by Ethical Committee of Wuhan University Zhongnan Hospital.

Conflicts of interest

The authors have no competing interests to declare.

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

Figures

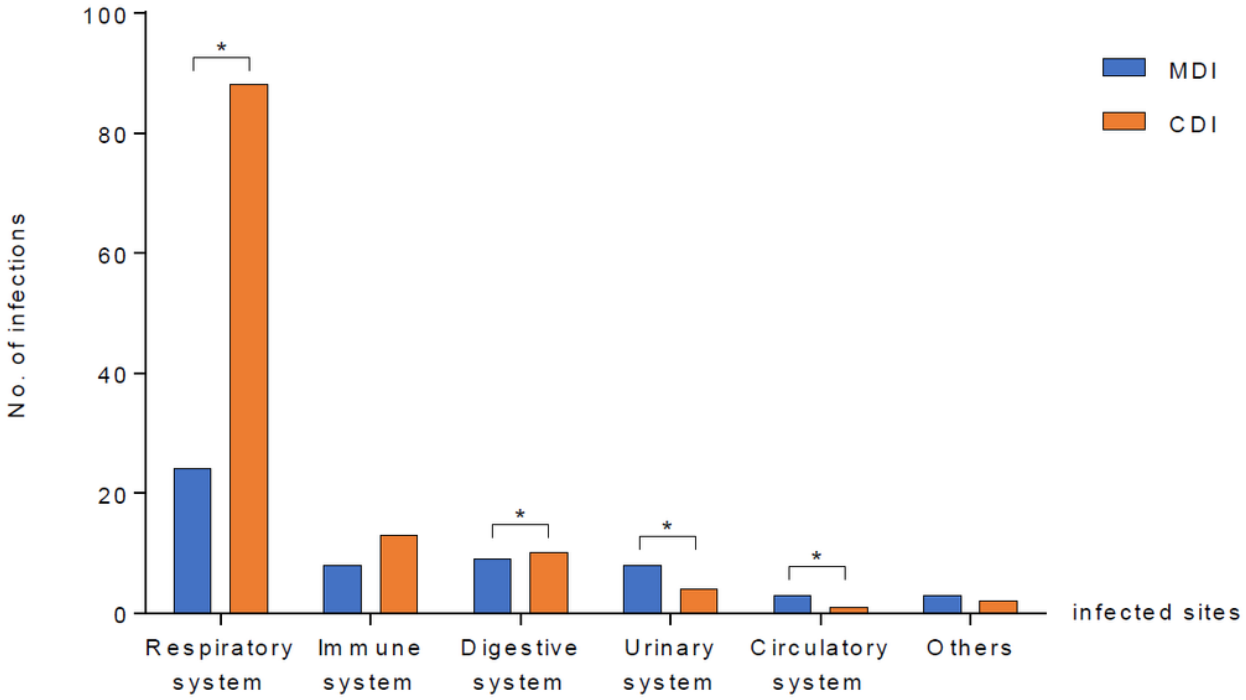

Figure 1

The distribution of infected sites

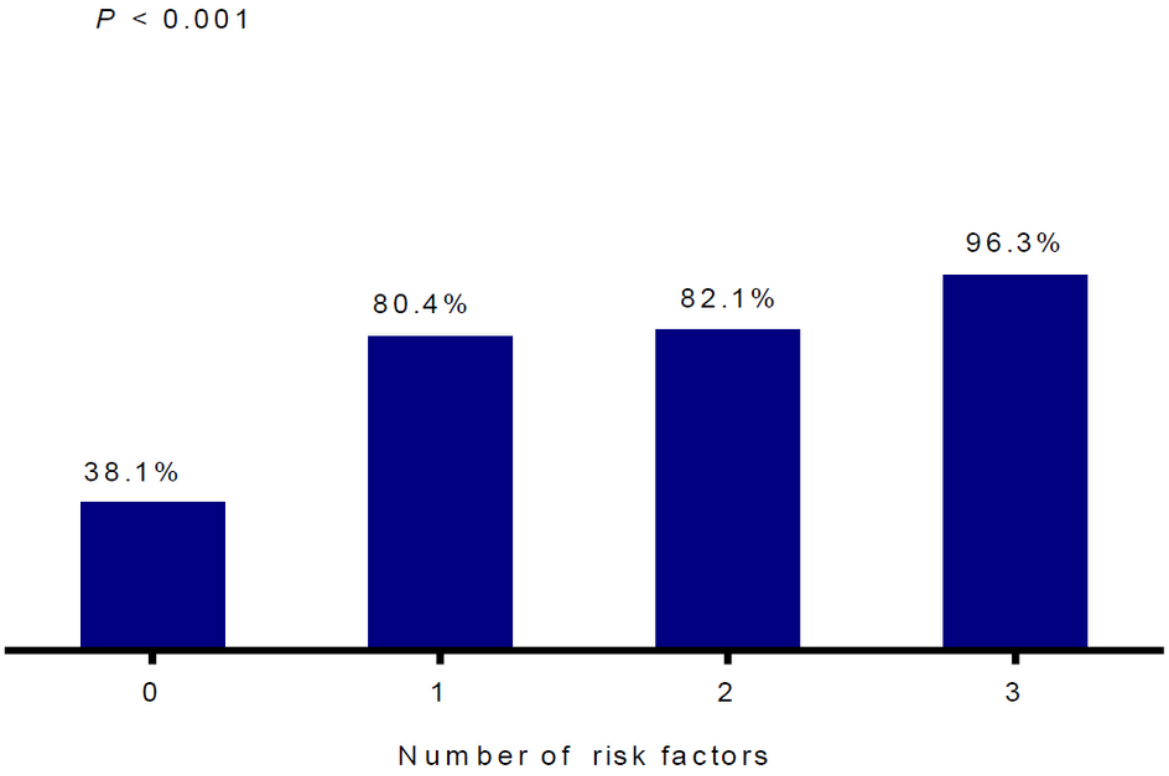

Figure 2

The probability of infection

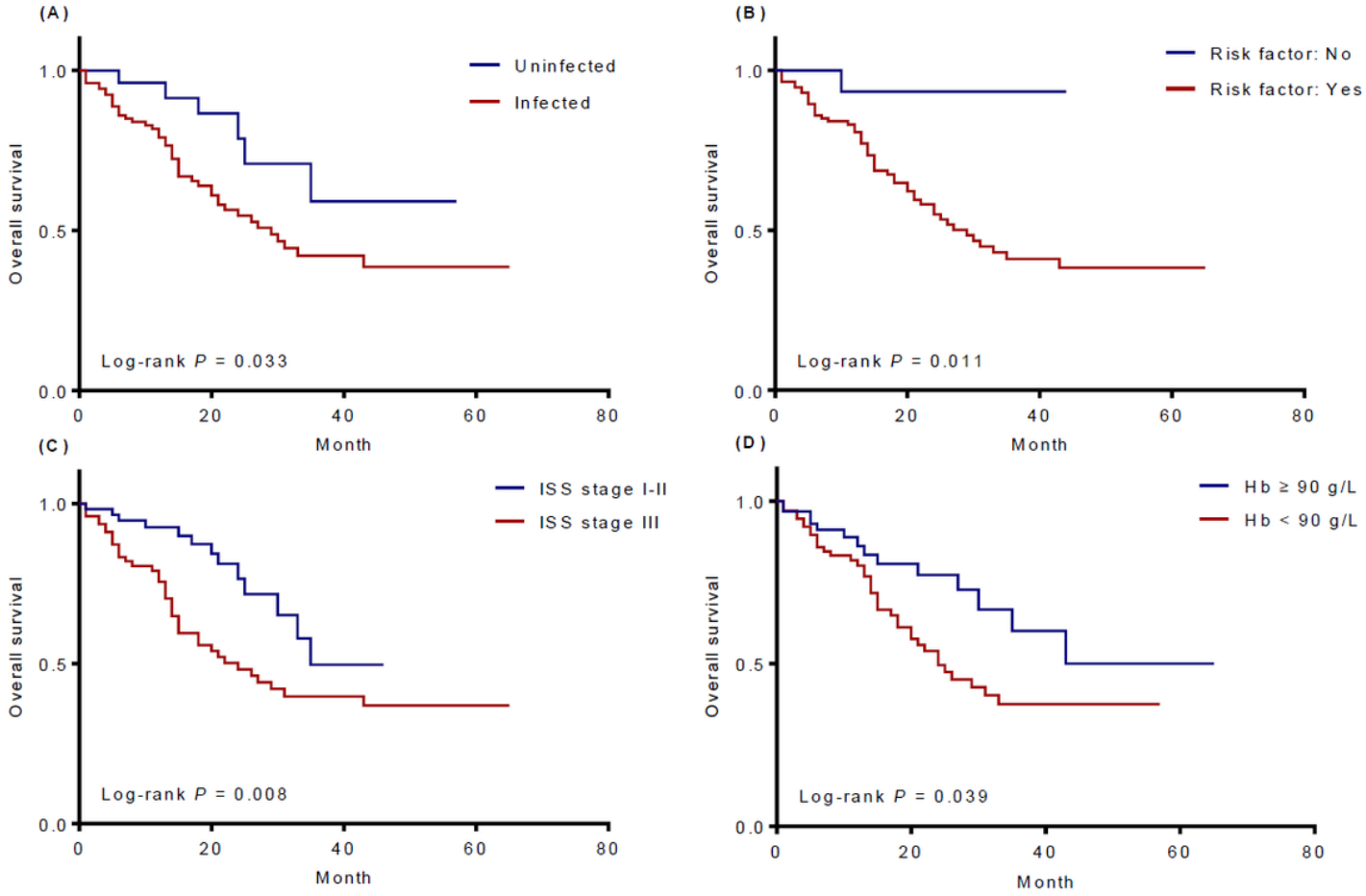

Figure 3

Kaplan Meier survival curve

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