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Infection in Multiple Myeloma: Microbiological Profile and Prognosis in Senegalese Patients

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Abstract

Introduction: Infections are additional factors of morbidity and mortality in multiple myeloma (MM), and the current recommendation is antibiotic prophylaxis. In sub-Saharan Africa, few data on infectious complications of MM are available. We aim to describe the microbiological features of infections in MM, and their impact on survival in Senegalese patients. **Methods**: A retrospective (January 2005-January 2022), analytic, multicenter study on infections in patients followed for MM (IMWG criteria) in Senegalese clinical hematology services. The socio-epidemiological, diagnostic, microbiological, evolutionary and survival aspects were analyzed. **Results**: The study included 106 patients with multiple myeloma who had an infection at admission or during the treatment. Ten patients have the comorbidity (hypertension, lupus, type 2 diabetes). These patients had 136 infectious events identified at diagnosis (79.2%) or during chemotherapy (20.8%). The sites of infection are lung (42.6%), urinary (29.4%), dermatological (6.6%), digestive (5.2%), osteoarticular (4.4%), ear, nose and throat (3.7%), central nervous system (1.5%), or without site. We recorded 26.4% of patients with multi-site infections. The causal pathogens are bacteria (Gram-negative bacilli: 22.1%; Gram positive bacilli: 9.5%, *Mycobacterium tuberculosis*: 13.3%), parasitique (plasmodium falciparum 6.6%), viruses (*SARS-COV2*: 2.9%, *VZV*: 2.2%) and fungal (2.9%). Survival was reduced in patients who had an infection at the time of multiple myeloma diagnosis (p: 0.189) and those who had multiple infectious foci (p: 0.011). **Conclusion:** Infections in multiple myeloma are more frequent at diagnosis. The germs are varied and mostly bacteria, particularly gram-negative bacteria, and *Koch*'s bacillus. Our study reveals that multiple infectious foci are a poor prognosis factor. It is necessary to evaluate the infectious risk early, and to adopt an antibiotic prophylaxis based on our tropical environment.

Keywords

Multiple Myeloma, Infections, Tuberculosis, Senegal

1. Introduction

Infections are commonly described during multiple myeloma (MM) [1] [2] [3], which is the more prevalent malignant plasma cell dyscrasia responsible for the secretion of monoclonal immunoglobulin. Infectious diseases in MM are related to the deficiency of humoral immunity, of B and T lymphocyte collaboration, of dendritic cells, and to the aggressiveness of the immunosuppressive drugs which are more and more innovative [2]. These factors reflect the infectious risk throughout the disease, from diagnosis to treatment. The germs are varied, and bacteria are found alongside viruses, fungi and parasites. The learned societies have written guidelines for the treatment of infections during MM [2]. Preventive treatment with quinolones is one of the main approaches, especially levofloxacin for neutropenic patients [4]. The problem of adapting these recommendations to our practice is increasingly essential. In sub-Saharan Africa, the authors [5] [6] [7] have mainly studied, the delay in diagnosis, the prognostic stage and the difficulty of access to innovative drugs as well as autologous hematopoietic stem cell transplantation. Data on infectious complications of MM are rarely available in the sub-Saharan literature [7] [8] [9]. Thus, we propose to describe the microbiological profile, the survival and its determinants in our practice of MM management.

2. Patients and Methods

Type and setting of the study: A retrospective and analytic study from January 2005 to January 2022 was conducted in two referral centers for inpatients and outpatients care of multiple myeloma in Senegal: Clinical Hematology Unit of Aristide le Dantec Hospital and Clinical Hematology Department of Dalal Jamm Hospital.

Patients: Patients were included the records of patients who were followed for MM according to the International Myeloma Working group criteria (IMWG dating from 2003 and 2014 [10] [11], and who had an infection at admission or during the course of treatment. In Senegal, preventive antibiotic therapy, and viral prophylaxis are not recommended, and not systematically applied for MM patients. The presence of clinical and/or radiological and/or microbiological signs associated with systemic inflammatory response syndrome was instead, depending on their location, in favor of an infectious focus, pulmonary, urinary, etc. The causative germs were identified by examination of fluids (sputum, urine, pus, joint fluid, etc) or by swabbing: bacteria by specific bacteriological testing, viruses such as *SARS-Cov*-2 (*Severe Acute Respiratory Syndrome Coronavirus*-2) demonstrated by polymerized chain reaction and fungi found on

mycological examination. Infection by *Plasmodium falciparum* was retained in case of positivity of the rapid diagnostic test and the examination of the blood smear by light microscopy. In cases where microbiology did not isolate a germ, the accountability of the infection was the clearance of the infectious site and disappearance of inflammatory syndrome under antibiotic therapy adapted to the ecology (site, temperature curve, antibiotics taken recently). Two or more concomitant infectious sites were classified as multi-site infection patients. Bacterial and fungal infections were treated according to the sensitivity of the drugs tested in laboratory, *SRAS-CoV*-2 infection was managed with analgesics associated with dexamethasone and oxygen therapy according to clinical severity. Malaria was treated with a combination of synthetic antimalarials. The management of MM in our setting, is done by multidrug therapy based on non-subsidized molecules, prescribed according to the patient's financial means. Thus, in our study, from 2005 to 2016, the MP (melphalan, prednisone) protocol was used, then since 2016, various molecules have become accessible (e.g Thalidomide: Thal, Bortezomib: V, Endoxan: C, Dexamethasone: Dex) and the protocols prescribed are MPThal, CTDex and VTDex. Autologous haematopoietic stem cell transplant is not available in Senegal.

Anonymity and confidentiality are guaranteed for all patients included in the study

Data Processing and Statistical Analysis: Epidemiological (age, gender), diagnostic (symptoms, biology or labs), prognosis (Salmon Durie [12], International Staging System (ISS) [13] and infectious (date of diagnosis, location, microbiology) variables were analysed. We expressed the numerical variables as means ± standard deviation, with the sample size (n), and we analyzed ordinal variables with the chi-square test.

For the evolutionary data, we assessed the therapeutic responses as [14]: complete remission (CR), Stringent complete response (SCR), partial remission (RP), very good response partial (VGRP), stable disease (SD), progressive disease (PD), relapse, deaths and lost patients. We defined remission (CR, SCR, RP, VGRP) and no remission (SD, PD, relapse). Outcome was assessed by median survival with quartile range (IQR) Kaplan Meier curve, and log Rank test (p). Patients who were lost to follow up were not included in the analysis. All analyses were performed using SPSS (Statistical Package for the Social Sciences) version 21.0 software. The values were considered statistically significant at p-value < 0.05.

3. Results

3.1. Sociodemographic Characteristic

Of the 271 patients followed up during our study period, we included 106 patients (39.1%) who had 136 infectious events. The mean age was 60.3 ± 10.2 years and the sex ratio was 0.93. Comorbidities were observed in 9.4% of cases: type 2 diabetes (5 cases), hypertension (4 cases), and lupus disease (1 case).

These infections were prevalent at diagnosis in 79.2% of cases and under chemotherapy in 20.8% of patients.

3.2. Characteristic of Patient with the Multiple Myeloma

Symptoms associated with infections (Table 1) were anemia (65.1%) and inflammatory pain (40.6%) next to complications such as slow cord compression (18.9%) and renal failure (9.4%). The median gammaglobulin level was 44.6 g/L (range: 4.8 - 98.8 g/L). Hypogammaglobulinemia was noted at diagnosis in 7 patients (6.6% of cases), with the mean of 4.2 ± 0.33 g/L. The myeloma was symptomatic with secretion of complete IgG (37.7%), to light chain kappa in 56.9% of patients. In 6.6% of the cases, free light chains were involved in patients with hypogammaglobulinemia.

Table 1. Diagnostic and evolutionary characteristics of the study population.

Parameters		Number (%)
Associated signs (N = 106)	Anemia	69 (65.1)
	Pain	43 (40.6)
	SCC	20 (18.9)
	Renal Failure	10 (9.4)
	Fracture	8 (7.5)
Paraprotein type: (N = 106)	IgG	40 (37.7)
	IgA	12 (11.3)
	IgD	1 (0.9)
	FLC	7 (6.6)
	Light chain kappa	61 (57.5)
	Light chain lambda	45 (42.5)
Salmon Durie: (n = 98)		
I-II		14 (14.3)
III		84 (85.7)
ISS: (n = 37)		
I-II		22 (59.5)
III		15 (40.5)
Treatment (N = 106)	MP	34 (32.1)
	MPT	28 (26.4)
	CTD	24 (22.6)
	VTD	20 (18.9)
Assessment on treatment: (n = 54)	CR	11 (20.3)
	PR	9 (16.7)
	VGPR	16 (29.6)
	PD	16 (29.6)
	SD	1 (1.9)
	Relapse	1 (1.9)
Death (N = 106)		32 (30.1)

MP: melphalan-prednisone; MPT: Melphalan-Prednisone-Thalidomide, CTD: Endoxan-Thalidomide-Dexamethasone; VTD: Bortezomib-Thalidomide Dexamethasone; FLC: free light Chains; CR: complete response; PR: partial response; VGPR: very good partial response; SD: stable disease; PD: progressive disease; SCC: spinal cord compression; ISS: International Staging System; Ig: Immunoglobulin; N: Total number, n: number concerned.

The patients were seen for the first time, in advanced stage according to ISS in 40.5% of the cases (Table 1).

3.3. Type of Infections and Causal Microbes

Signs of infection were a reason for consultation in (79.2%) cases or occurred during chemotherapy (20.8%). The systemic inflammatory response syndrome was associated with organ involvement (Table 2) such as pulmonary (42.6%), urogenital (29.4%), dermatological (6.6%) and digestive (5.2%), or was isolated (6.6%). In some cases (26.4%), the patient had multi-site infection during follow-up. The microbes found (Table 2) in 54.9% of cases were bacteria, with Gram-negative bacilli (22.1%), including *E. coli* in 14.7% of cases, Gram-positive bacilli (9.5%) and *Koch's bacilli* (13.3%). The other microbes were, parasitic (6.6%), viruses (5.1%) and fungal (2.9%).

Table 2. Distribution of microbes according to their location, of the study population.

Germs	locations of infections								Total n (%)
	Lun n (%)	Urin n (%)	ENT n (%)	Derm n (%)	Diges n (%)	Ménin n (%)	Os-art n (%)	SIRS n (%)	
E. coli		17 (12.5)			2 (1.5)		1 (0.7)		20 (14.7)
K. pn	3 (2.2)								3 (2.2)
P. aer		1 (0.7)		1 (0.7)					2 (1.5)
P mir		2 (1.5)							2 (1.5)
C. fr		2 (1.5)							2 (1.5)
K. oxy		1 (0.7)							1 (0.7)
S. au	4 (2.9)	3 (2.2)	2 (1.5)	2 (1.5)					11 (8.1)
G.vag		1 (0.7)							1 (0.7)
E. fae					1 (0.7)				1 (0.7)
B. k	11 (8.2)	1 (0.7)		1 (0.7)		2 (1.5)	3 (2.2)		18 (13.3)
SRAS-Cov-2	4 (2.9)								4 (2.9)
VZV				3 (2.2)					3 (2.2)
C.alb				1 (0.7)	3 (2.2)				4 (2.9)
P fal								9 (6.6)	9 (6.6)
N R	36 (26.4)	12 (8.9)	3 (2.2)	1 (0.7)	1 (0.7)		2 (1.5)		55 (40.5)
Total	58 (42.6)	40 (29.4)	5 (3.7)	9 (6.6)	7 (5.2)	2 (1.5)	6 (4.4)	9 (6.6)	136 (100)

n: number concerned; NR: negative microbiology; lun: lungs; ur: urogenital; ENT: Ear, Nose and Throat; Derm: dermatological; Diges: digestive, menin: meningeal; os art: osteo articular; SIRS: systemic inflammatory response syndrome; *E. coli*: *Escherichia coli*; *K. pn*: *Klebsiella pneumoniae*; *P. aer*: *Pseudomonas aeruginosa*; *P mir*: *Proteus mirabilis*; *C. fr*: *Citrobacter freundii*; *K. oxy*: *Klebsiella oxytoca*; *S. au*: *Staphylococcus aureus*; *G.vag*: *Gardnerella vaginalis*; *E. fae*: *Enterococcus faecalis*; *B. k*: *Koch's bacillus*; *VZV*: *varicella-zoster virus*; *C alb*: *candida albicans*; *SRAS-CoV*-2: *severe acute respiratory syndrome coronavirus 2*; *P fal*: *Plasmodium falciparum*; Gram-negative bacteria: *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella oxytoca* , *Klebsiella pneumoniae*, *Citrobacter freundii*, *Gardnerella vaginalis*; Gram-positive bacteria: *Enterococcus faecalis*, *Staphylococcus aureus*.

The analysis of the distribution of microbes according to the outbreaks (Table 2) noted that undocumented pneumonia represented 26.4% of cases, alongside tuberculosis in 8.2% and *SARS-Cov*-2 (2.9%). Gram-negative bacteria were responsible for urinary tract infection in 16.9% of cases. We found 5.1% of patients with extra pulmonary tuberculosis. Fungal infections (2.9%) were dermatological and digestive. The blood smear was positive and isolated *Plasmodium falciparum* in 6.6% of patients who had an isolated fever.

3.4. Evolution of the Diseases with Infections Event

The outcomes (Table 1) concern 54 (50.9%) patients regularly followed, of whom 66.6% were in remission. Patients lost to sight were 49.1% of cases. The death became in 30.1% of cases with 15.4% are related to infection: the germs identified were Gram negative bacilli (7.7%), *Koch's bacilli* (4.6%) and *SARS-Cov*-2 (3.1%).

3.5. Association between Infection Event and the Outcome of Multiple Myeloma

In univariate analysis (Table 3), infections occurring during chemotherapy were observed in subjects under 60 years of age (p: 0.025) and who also developed multi-site infections (p: 0.049). The hemoglobin level was 9.7 g/dl at diagnosis and 8.9 g/dl in patients who had an infection during chemotherapy (p: 0.032). Prognosis score (ISS) and hypercalcemia, were not decisive for the timing and severity of infections (Table 3). In patients who had a multi-site infection, remission was achieved in 11.11% of cases and absent in 33.3% of cases (p: 0.056).

Table 3. Epidemiological, biological, and survival profile according to time of onset and number of infection site, of the study population.

Parameters	Date of infection		p	Number of site		p
	At diagnosis	Under chemotherapy		Single	Multiple	
AGE (year): Mean ± SD	60.4 ± 10.4	59.8 ± 9.7	0.025	60.3 ± 0.3	59.4 ± 10.0	0.049
Hb (g/dl) Mean ± SD	9.7 ± 3.1	8.9 ± 3.0	0.032	9.5 ± 2.6	8.2 ± 2.8	0.165
MCV (fl) Mean ± SD	86.6 ± 7.1	90.0 ± 8.7	0.107	91.5 ± 8.9	81.8 ± 21.2	0.305
WBC (G/L) Mean ± SD	6.9 ± 2.8	9.1 ± 3.9	0.761	7.3 ± 3.1	7.3 ± 3.2	0.979
C Calcemia (mg/l) Mean ± SD	121.2 ± 38.2	108.4 ± 13.9	0.154	134.3 ± 27.1	104.7 ± 35.4	0.432
ISS I-II n (%)	18 (81.1)	4 (18.9)	0.412	18 (81.8)	4(18.2)	0.532
ISS III n (%)	11 (73.3)	4 (26.7)		13 (86.7)	2 (13.3)	
Remission n (%)	28 (77.8)	8 (22.2)	0.463	32 (88.9)	4 (11.1)	0.056
No remission n (%)	15 (83.3)	3 (16.7)		12 (66.7)	6 (33.3)	

C Calcemia: corrected serum calcemia with albumin; SD: standard deviation, Hb: haemoglobin; MCV: mean corpuscular volume; WBC: white blood cells; p: p-value. ISS: International Staging System.

The duration of follow-up was on average 45.4 months with extremes of 0.7 months and 112.9 months. The median of survival if the infection appeared at admission was 32.4 ± 15.7 months (IQR: 1.6 - 63.2), compared to 45.5 ± 12.8 months (IQR: 20.3 - 70.6) if it occurred during chemotherapy. The overall survival at 2 years was 58.2% in patients who had an infection at diagnosis, and 65% for those who had infectious foci during chemotherapy (**Figure 1**) (p: 0.189).

Depending on the number of infectious outbreaks, the median survival was 45.5 months (IQR: 22.6 - 68.3) if single site, compared to 16.5 months (IQR: 4.5 - 25.2) if the locations were multiple. The study of the survival curve according to location (**Figure 2**), showed an overall survival at 2 years was 81% for patients who had a single location, and 42% for those who had several infectious foci. (p: 0.011).

4. Discussion

In sub-Saharan Africa, data on infections during MM are poorly documented: not reported in some publications [8] [9] and sometimes only frequencies are published [5] [15] [16]. For example, in Senegal, 23% of patients followed for MM had an opportunistic infection at diagnosis [15]. In Côte-d'Ivoire [5], infections represented 27% of complications in patients under 60 years of age undergoing chemotherapy. Okella *et al.* [16] reported 6 cases of *HIV* in a total of 217 patients, without any information on the stage of the disease and/or associated opportunistic infections. We report the largest series of infection during MM (39.1%) in sub-Saharan Africa. In our setting, the difficulties to have data on infections during MM could be explained by the initial consultation in infectious diseases services and by the difficulties to isolate the germ. Microbiologically undocumented infections are common in MM, and Valković T *et al.* [17] published 37.2% of negative cultures in his cohort of patients followed in hospital. The negativity of the microbiology should not be a brake to the management, and the accountability should be done by the absence of other etiologies responsible for the systemic response syndrome.

Concerning the epidemiological aspects, our study population is composed of adults in their sixties, in accordance with the literature on MM in Africa [5] [8] [18]. A female predominance is observed in our series as the same of Valković T *et al.* [17], probably related to the greater susceptibility to make urinary infections.

Regarding the diagnostic aspects, the occurrence of infections is described throughout the disease. In our study, this infectious complication is more frequent at the time of diagnosis and is associated with a decrease survival rate. This peak in frequency at diagnosis is due to the fact that our patients consult late with a difficult circuit [6], responsible for advanced forms of the disease at the stage of high tumor burden [5] [6] [8]. Also, complications such as impaired renal function and spinal cord compression are respectively factor for decreased immunity and infection [2]. Thus, in our study, high tumor burden, spinal cord compression and chronic kidney disease which are recognized as the main factors favoring infections [1] [2] were combined in our patients.

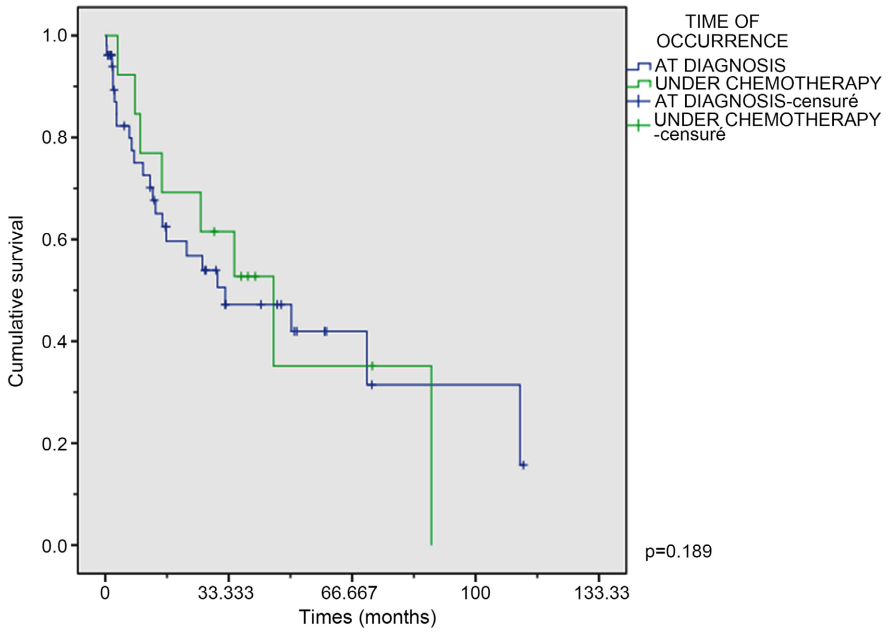

Figure 1. Survival curve of patients according to the time the infection occurred, of the study population.

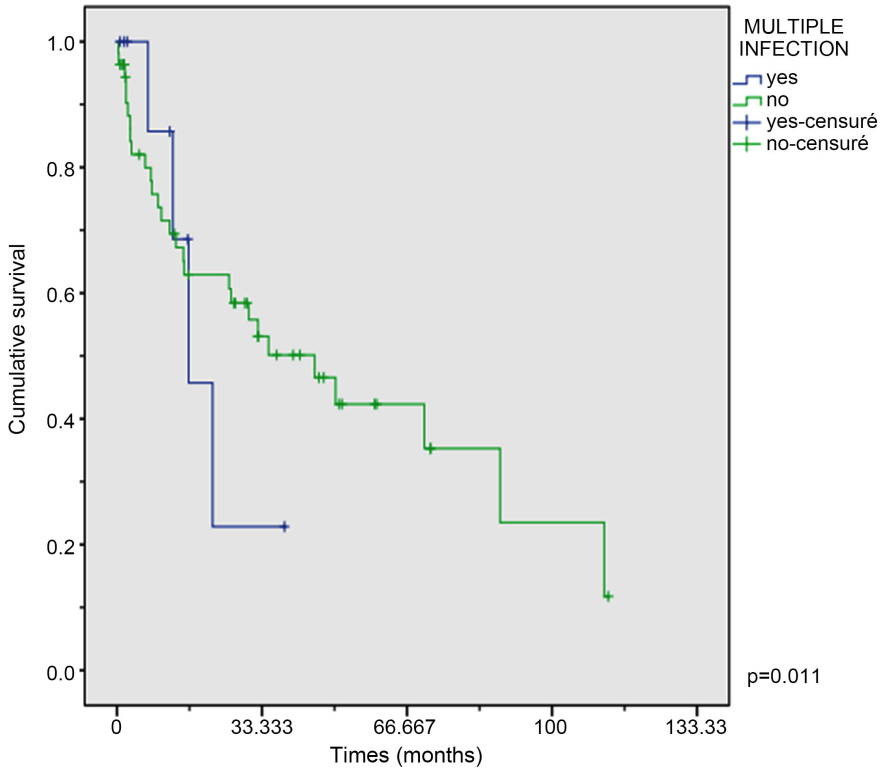

Figure 2. Survival curve of patients according to the number of infectious sites, of the study population.

Also, survival is impaired when infection occurs during chemotherapy [1] [2]. Some molecules have a high immunosuppressive capacity and their mechanism of action explains the nature of fearsome microbes [1] [2] [19]. Thus, an increase

in infections is expected in the course of these treatments. This last aspect was not found in our series with less than third of the patients who had an infection in the follow-up. This could be explained, in our context by the difficulty to access of innovative treatment. On the other hand, aggressive chemotherapy aimed at obtaining pre-transplant remission expose young subjects to superinfection [19] [20]. We do not perform autograft of hematopoietic stem cells in our setting in Senegal. However the recurrence of infection in young subjects is seen in our study like Tolo A *et al.* [5] who described a frequency of 33% in his cohort.

Regardless of the onset time of the infection, patients present a diversity of infectious foci. Pulmonary infections dominated in our study, as well as in the publication by Zahid MF *et al.* [21] who reported 35.7% of infectious lung diseases.

Our study shows a high frequency of microbiologically negative lung infections; this is partly related to the self-medication [6]. Koch's bacillus is the predominant germ isolated in the lungs, and is a factor of postponement of chemotherapy, which worsens morbidity and mortality. Besides chronic infections, our patients are exposed to SRAS-CoV-2 responsible for serious pandemic emerging infection during MM [22]. Besides the lung, the second most common site of infection is genitourinary in our patients (22.3%) and in the study of Djebbari F *et al.* (33.3%) [23]. In contrast, the urinary site dominated in the cohort of hospitalized patients with indwelling urinary catheters [17]. The most frequent microbes are gram-negative bacilli, particularly *E. coli* and *P. aeruginosa* [17] [20], like in our study. Other sites (dermatological, digestive, meningeal and osteoarticular) are not rare and have been reported in the literature [20]. The diversity of germs, testifies to the variability of the mechanisms of immunosupression in MM [1] [2] and environmental factors partly responsible for malaria. However, some microbes have a particular localization and our study shows the same feature: gram negative bacteria are more isolated in the genito-urinary tract, beside to viruses and candida in dermatological diseases [17] [19] [20]. Tuberculosis is more localized in the lungs [17], the extra pulmonary form described in our series of patients remains rare. Even if the ecology of the germs is known, the difficulties of access to a microbiological diagnosis by molecular biology, explains that only the serological forms, or morphological identification of the germ is documented in our practices. The systematic search for infection by clinical examination, and a laboratory assessment oriented according to the existence of predictive factors, would be useful for an early diagnosis and a better control of the ecology of the germs in our patients.

These infections reduce survival and cause high mortality [3] [21] [22] [23], especially since they appear early and found in multiple sites. Toni Valković T *et al.* [17], observed a mortality of 9.3% in patients reinfected after a first infectious episode. Multisite locations were also associated with a significant reduction in survival in our patients. Prognosis by ISS did not have an impact survival in our setting.

Limitations of Study

We have observed many infections with negative microbiology, related to non-performing exploration platforms available in our countries. The number of loss to follow-up makes our statistical analysis weak; this is related to the absence of decentralized hematological structures outside of reference hospitals, and a single medical file for adequate referral of patients followed for MM.

5. Conclusion

Infections are more frequent at the time of diagnosis in the context of advanced disease. Our study reports a varied profile of microbes which dominated by bacteria, particularly gram-negative bacteria and Koch's bacillus. Also, infection observed at the time of diagnosis and the multisite location are factors reducing survival. In our practice, to improve prognosis, it is necessary to assess the infectious risk at an early stage and to adopt anti-infectious prophylaxis based on microbiological ecology in our tropical environment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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