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Clinical impacts of delayed central venous catheter removal according to the severity of comorbidities in patients with candidaemia

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SUMMARY

Background: The effects of early central venous catheter (CVC) removal on the clinical outcomes of patients with candidaemia remain controversial. This study evaluated the impact of delayed CVC removal on mortality according to the severity of comorbidities in patients with candidaemia.

Methods: Patients with candidaemia in a tertiary care hospital between January 2010 and December 2017 were included retrospectively. The severity of comorbidities was classified as low [Charlson Comorbidity Index (CCI) score $\leq$3] or high (CCI score $\geq$4). Cases with removal of CVC $>$2 days after the onset of candidaemia or without CVC removal were classified as having delayed CVC removal.

Results: In total, 239 patients with candidaemia were included, excluding 18 who died within 2 days of onset of candidaemia. Of these, 149 had low CCI scores and 90 had high CCI scores. Septic shock [adjusted odds ratio (aOR)=9.5] and delayed CVC removal (aOR=4.7) were significantly associated with increased 30-day mortality, whereas *Candida parapsilosis* infection (aOR=0.2) and cerebrovascular disease (aOR=0.3) were associated with decreased 30-day mortality, in patients with low CCI scores. Septic shock (aOR=13.0) was the only risk factor for 30-day mortality in those with high CCI scores. Delayed CVC removal was associated with increased 30-day mortality in patients with low CCI scores (50.0% vs 20.3%; P=0.001), but not in those with high CCI scores (50.0% vs 47.9%; P=0.87).

Conclusion: Early CVC removal may improve the survival of patients with candidaemia and low CCI scores, but no such protective effect was evident in those with high CCI scores.

Introduction

Candidaemia is a significant hospital-acquired bloodstream infection associated with substantial morbidity and mortality [1,2]. It can develop through gastrointestinal tract mucosal translocation of colonized *Candida* spp. by disruption of mucosal barriers or loss of the attributable host defence mechanisms,

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especially in neutropenic or intensive care unit (ICU) patients [3]. However, the major source of candidaemia is intravascular catheters, especially central venous catheters (CVCs), as *Candida* spp. are able to bypass the host barriers and enter the bloodstream directly [4,5]. At least 70% of non-neutropenic patients who develop candidaemia have CVCs *in situ* [6–8]. CVC removal from a patient with candidaemia is recommended if the CVC is presumed to be the source of infection [9]. However, catheter-related infections are difficult to distinguish from those arising from gastrointestinal tract penetration.

Many reports have shown that CVC removal improves clinical outcomes, including mortality and persistent infection [10–13]. Catheter-related candidaemia is associated with biofilm formation, and antifungal therapy alone (without CVC removal) may not cure the condition [14]. Removal of the source of infection reduces the mycological burden [15,16]. However, the effects of early CVC removal on the clinical outcomes of patients with candidaemia remain controversial. Some studies have shown that early CVC removal enhances survival [11,17]. However, Rodriguez *et al*. reported that early CVC removal did not confer a significant survival benefit, and removal decisions should be based on the risks and possible benefits in individual patients [18]. The discrepancy of results suggests that early CVC removal is potentially useful in specific patient populations.

The Charlson Comorbidity Index (CCI) is commonly used to access the severity of underlying diseases [19]. The CCI score correlates with mortality. The objective of this study was to evaluate the impact of delayed CVC removal on clinical outcomes according to the severity of comorbidities (CCI score) in patients with candidaemia.

Methods

Study population

All adult patients with candidaemia treated between January 2010 and December 2017 at a tertiary care hospital in South Korea were included. The medical records of all subjects were reviewed retrospectively. The study was approved by Kyung Hee University Hospital Institutional Review Board.

Definitions

Candidaemia was defined as isolation of *Candida* spp. from at least one blood culture, combined with symptoms and signs of bloodstream infection. The CCI score was used to estimate the severity of comorbidities [19]. A low CCI score was defined as $\leq$3 and a high CCI score was defined as $\geq$4. Definite CVC-related candidaemia was defined when both blood and catheter tip cultures yielded the same *Candida* spp., or the same species grew in CVC and peripheral vein blood cultures with positive values for differential time to positivity. Probable CVC-related candidaemia was defined as a positive blood culture but no obvious catheter site infection and a negative semi-quantitative culture. When the infection site could not be identified, it was recorded as 'unknown'. Complications of candidaemia included septic thrombophlebitis, infective endocarditis, septic pneumonia, endophthalmitis, osteomyelitis and deep tissue abscesses.

Eradicable infection sources included surgically removable infections, drainable abscesses and indwelling foreign bodies, such as peripheral line catheters and CVCs [20]. Patients with early removal of an eradicable infection source (including CVCs) were defined as those who had the infection source removed within 2 days of the onset of candidaemia (at the time of blood culture). Cases with removal of eradicable infection source including CVC >2 days after the onset of candidaemia (at the time of blood culture) or without removal of infection source were classified as having delayed removal of eradicable infection source. Appropriate initial antifungal therapy was defined as the prescription of at least one in-vitro-active antifungal agent on the day of or 2 days after the index blood culture. Appropriate definitive antifungal therapy was defined as the use of an antifungal agent to which the cultured *Candida* spp. was known to be susceptible.

Statistical analysis

All statistical analyses were performed using SPSS for Windows Version 22.0K (IBM Corp., Armonk, NY, USA). Categorical variables were compared using the Pearson χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann–Whitney *U*-test. To identify independent risk factors for 30-day mortality, all variables significant in univariate analyses were included in a multi-variable logistic regression model. Variables exhibiting high-level multi-collinearity were excluded from the final model. All statistical tests were two tailed, and *P*-values $\leq$0.05 were considered to indicate statistical significance. Kaplan–Meier survival analysis was used to determine the time to 30-day mortality in patients undergoing early and delayed CVC removal according to the severity of comorbidities. Kaplan–Meier estimates were compared using the log-rank test.

Results

Clinical characteristics by severity of comorbidities

In total, 257 patients with candidaemia during the study period were identified. The 18 patients who died within 2 days of onset of candidaemia were excluded because they could not be assigned to the early or delayed catheter removal group. Ultimately, data from 239 patients were analysed; 149 (62.3%) of these patients had low CCI scores and 90 (37.7%) had high CCI scores. Patients' demographic characteristics are shown according to severity of comorbidities in Table I. The patients with low CCI scores were more likely than those with high CCI scores to have cerebrovascular disease and haematologic malignancies, and less likely to have solid tumours, liver cirrhosis and end-stage renal disease. CVCs were present at the onset of candidaemia in 76.2% of patients; the frequencies were similar in both groups. CVC-related candidaemia (68.2%) was the most common source of infection, followed by intra-abdominal (3.8%) and urinary tract infections (3.8%). The most frequently isolated organism was *Candida albicans*, followed by *Candida tropicalis, Candida parapsilosis* and *Candida glabrata*; the species distributions did not differ significantly between groups.

Risk factors for 30-day mortality

The in-hospital, 14-day and 30-day mortality rates for patients with candidaemia were 48.5% (116/239), 25.1% (60/

Table I
Demographic characteristics of patients with candidaemia according to the severity of comorbidities

Characteristic	Total	Low CCI (scores ≤3) (*N*=149)	High CCI (scores ≥4) (*N*=90)	*P*
Age, median (IQR)	70 (61–76)	71 (61–77)	67 (60–74)	0.048
Male gender	122 (51.0)	74 (49.7)	48 (53.3)	0.58
Underlying diseases				
Cerebrovascular disease	92 (38.5)	72 (48.3)	20 (22.2)	<0.001
Solid tumour	104 (43.5)	35 (23.5)	69 (76.7)	<0.001
Diabetes mellitus	84 (35.1)	47 (31.5)	37 (41.1)	0.13
Haematologic malignancy	20 (8.4)	17 (11.4)	3 (3.3)	0.03
Liver cirrhosis	16 (6.7)	3 (2.0)	13 (14.4)	<0.001
End-stage renal disease	11 (4.6)	2 (1.3)	9 (10.0)	0.002
Chronic heart failure	9 (3.8)	7 (4.7)	2 (2.2)	0.49
Underlying condition				
ICU stay at onset of candidaemia	62 (25.9)	44 (29.5)	18 (20.0)	0.10
Previous immunosuppressant use	5 (2.1)	3 (2.0)	2 (2.2)	>0.99
Neutropenia (ANC <500 cells/mm^3)	12 (5.0)	10 (6.7)	2 (2.2)	0.22
Previous surgery within 1 month	75 (31.4)	59 (39.6)	16 (17.8)	<0.001
Previous chemotherapy within 1 month	29 (12.1)	13 (8.7)	16 (17.8)	0.04
Mechanical ventilation on the day of candidaemia	54 (22.6)	39 (26.2)	15 (16.7)	0.09
Renal replacement therapy on the day of candidaemia	20 (8.4)	9 (6.0)	11 (12.2)	0.09
Candida spp.				
C. albicans	121 (50.6)	76 (51.0)	45 (50.0)	0.88
C. tropicalis	44 (18.4)	28 (18.8)	16 (17.8)	0.85
C. parapsilosis	40 (16.7)	25 (16.8)	15 (16.7)	0.98
C. glabrata	29 (12.1)	16 (10.7)	13 (14.4)	0.40
Others[a]	5 (2.1)	4 (2.7)	1 (1.1)	0.65
Polymicrobial bloodstream infection	29 (12.1)	17 (11.4)	12 (13.3)	0.66
Septic shock	82 (34.3)	47 (31.5)	35 (38.9)	0.25
Central venous catheter placement	182 (76.2)	110 (73.8)	72 (80.0)	0.28
Source of infection				
Unknown	54 (22.6)	37 (24.8)	17 (18.9)	0.29
Definite CVC-related candidaemia	100 (41.8)	65 (43.6)	35 (38.9)	0.47
Probable CVC-related candidaemia	63 (26.4)	32 (21.5)	31 (34.4)	0.03
Intra-abdominal infection	9 (3.8)	6 (4.0)	3 (3.3)	>0.99
Urinary tract infection	9 (3.8)	4 (2.7)	5 (5.6)	0.30
Peripheral catheter-related candidaemia	2 (0.8)	2 (1.3)	0	0.53

CCI, Charlson Comorbidity Index; IQR, interquartile range; ICU, intensive care unit; ANC, absolute neutrophil count; CVC, central venous catheter. Data are presented as no. (%) of patients, unless otherwise indicated.

[a] *C. guilliermondii* (*N*=2), *C. lusitaniae* (*N*=1) and *C. pelliculosa* (*N*=1) were included in patients with low CCI scores, and *C. famata* (*N*=1) was included in those with high CCI scores.

239) and 37.7% (90/239), respectively. Univariate analysis indicated that CCI score was associated with increased 30-day mortality of patients with candidaemia [odds ratio (OR) 1.21, 95% confidence interval (CI) for one-point increment 1.07–1.37; *P*=0.002], whereas this association was not evident on multi-variate analysis. Patients with high CCI scores had a higher 30-day mortality rate than patients with low CCI scores [47.8% (43/90) vs 31.5% (47/149); *P*=0.01].

The risk factors for 30-day mortality in 239 patients with candidaemia, excluding 18 patients who died within 2 days of onset of candidaemia, are listed according to the severity of comorbidities in Table II. Univariate analysis revealed that haematologic malignancies, previous use of immunosuppressants, neutropenia, prior history of chemotherapy, mechanical ventilation on the day of candidaemia diagnosis, *C. tropicalis* bloodstream infection, septic shock and delayed CVC removal were significantly associated with increased 30-day mortality in patients with low CCI scores. Cerebrovascular disease and *C. parapsilosis* bloodstream infection were associated with decreased 30-day mortality in such patients on univariate analysis. On multi-variate analysis, septic shock [adjusted odds ratio (aOR)=9.5; 95% CI 3.3–27.7] and delayed CVC removal (aOR=4.7; 95% CI 1.7–13.3) were independently associated with increased 30-day mortality, whereas *C. parapsilosis* infection (aOR=0.2; 95% CI 0.03–0.8) and cerebrovascular disease (aOR=0.3; 95% CI 0.1–0.8) were associated with decreased 30-day mortality, in patients with low CCI scores (Table III). Definite CVC-related candidaemia was more common and septic shock was less common in patients infected with *C. parapsilosis* compared with those infected with other species. On univariate analysis, septic shock and CVC removal were significantly associated with 30-day mortality in patients with high CCI scores. On multi-variate analysis, septic shock (aOR=13.0; 95% CI 3.8–44.5)

Table II
Risk factors associated with 30-day mortality in patients with candidaemia according to the severity of comorbidities

Characteristic	Low CCI (scores ≤3)		*P*	High CCI (scores ≥4)		*P*
	Survivor (*N*=102)	Non-survivor (*N*=47)		Survivor (*N*=47)	Non-survivor (*N*=43)	
Age, median (IQR)	71 (61–76)	72 (60–81)	0.11	65 (57–73)	70 (62–75)	0.08
Male gender	49 (48.0)	25 (53.2)	0.56	25 (53.2)	23 (53.5)	0.98
Underlying diseases						
Cerebrovascular disease	55 (53.9)	17 (36.2)	0.04	12 (25.5)	8 (18.6)	0.43
Solid tumour	20 (19.6)	15 (31.9)	0.10	36 (76.6)	33 (76.7)	0.99
Diabetes mellitus	32 (31.4)	15 (31.9)	0.95	21 (44.7)	16 (37.2)	0.47
Haematologic malignancy	2 (2.0)	15 (31.9)	<0.001	1 (2.1)	2 (4.7)	0.60
Liver cirrhosis	3 (2.9)	0	0.55	8 (17.0)	5 (11.6)	0.47
End-stage renal disease	2 (2.0)	0	>0.99	4 (8.5)	5 (11.6)	0.73
Chronic heart failure	6 (5.9)	1 (2.1)	0.43	0	2 (4.7)	0.23
Underlying condition						
ICU stay at onset of candidaemia	28 (27.5)	16 (34.0)	0.41	9 (19.1)	9 (20.9)	0.83
Previous immunosuppressant use	0	3 (6.4)	0.03	2 (4.3)	0	0.50
Neutropenia (ANC <500 cells/mm^3)	2 (2.0)	8 (17.0)	0.001	1 (2.1)	1 (2.3)	>0.99
Previous surgery within 1 month	43 (42.2)	16 (34.0)	0.35	11 (23.4)	5 (11.6)	0.14
Previous chemotherapy within 1 month	3 (2.9)	10 (21.3)	0.001	11 (23.4)	5 (11.6)	0.14
Mechanical ventilation on the day of candidaemia	20 (19.6)	19 (40.4)	0.01	5 (10.6)	10 (23.3)	0.11
Renal replacement therapy on the day of candidaemia	4 (3.9)	5 (10.6)	0.14	3 (6.4)	8 (18.6)	0.08
Candida spp.						
C. albicans	50 (49.0)	26 (55.3)	0.48	21 (44.7)	24 (55.8)	0.29
C. tropicalis	14 (13.7)	14 (29.8)	0.02	9 (19.1)	7 (16.3)	0.72
C. parapsilosis	23 (22.5)	2 (4.3)	0.01	8 (17.0)	7 (16.3)	0.93
C. glabrata	11 (10.8)	5 (10.6)	0.98	9 (19.1)	4 (9.3)	0.18
Septic shock	17 (16.7)	30 (63.8)	<0.001	7 (14.9)	28 (65.1)	<0.001
Central venous catheter placement	74 (72.5)	36 (76.6)	0.60	37 (78.7)	35 (81.4)	0.75
Source of infection						
Unknown	21 (20.6)	16 (34.0)	0.08	7 (14.9)	10 (23.3)	0.31
Definite catheter-related candidaemia	48 (47.1)	17 (36.2)	0.21	19 (40.4)	16 (37.2)	0.76
Probable catheter-related candidaemia	22 (21.6)	10 (21.3)	0.97	15 (31.9)	16 (37.2)	0.60
Intra-abdominal infection	3 (2.9)	3 (6.4)	0.38	2 (4.3)	1 (2.3)	>0.99
Urinary tract infection	3 (2.9)	1 (2.1)	>0.99	4 (8.5)	1 (2.3)	0.36
Peripheral catheter-related candidaemia	2 (2.0)	0	>0.99	0	0	NC
Complication of candidaemia	11 (10.8)	6 (12.8)	0.72	9 (19.1)	6 (14.0)	0.51
Thrombophlebitis	3 (2.9)	0	0.55	0	0	NC
Endocarditis	0	0	NC	0	0	NC
Endophthalmitis	4 (3.9)	1 (2.1)	>0.99	4 (8.5)	1 (2.4)	0.36
Septic pneumonia	2 (2.0)	5 (10.6)	0.03	3 (6.4)	4 (9.3)	0.71
Removal of CVC in patients with CVC	70/74 (94.6)	28/36 (77.8)	0.02	33/37 (89.2)	23/35 (65.7)	0.02
Time to CVC removal (days), median (IQR)	2 (1–3)	3 (2–5)	0.003	3 (2–6)	2 (1–4)	0.19
Delayed CVC removal (>2 days)	23/74 (31.1)	23/36 (63.9)	0.001	25/37 (67.6)	23/35 (65.7)	0.87
Removal of CVC in patients with CRI	66/70 (94.3)	20/27 (74.1)	0.01	32/34 (94.1)	22 (68.8)	0.01
Time to CVC removal (days), median (IQR)	2 (1–3)	2 (2–5)	0.03	3 (2–6)	3 (2–4)	0.22
Delayed CVC removal (>2 days)	23/70 (32.9)	16/27 (59.3)	0.02	23/34 (67.6)	21/32 (65.6)	0.86
Removal of eradicable infection source, including CVC	73/77 (94.8)	21/29 (72.4)	0.003	35/38 (92.1)	22/32 (68.8)	0.01
Time to removal of eradicable infection source (days), median (IQR)	2 (1–3)	2 (2–6)	0.02	3 (2–6)	3 (2–4)	0.19
Delayed removal of eradicable infection source (>2 days)[a]	26/77 (33.8)	17/29 (58.6)	0.02	25/38 (65.8)	21/32 (65.6)	0.99

(*continued on next page*)

Table II (*continued*)

Characteristic	Low CCI (scores ≤3)		*P*	High CCI (scores ≥4)		*P*
	Survivor (*N*=102)	Non-survivor (*N*=47)		Survivor (*N*=47)	Non-survivor (*N*=43)	
Removal of eradicable infection source, excluding CVC	7/7 (100)	1/2 (50.0)	0.22	3/4 (75.0)	0/0	NC
Time to removal of eradicable infection source (days), median (IQR)	0 (0–6)	11 (11–11)	0.25	9 (0–9)	NC	NC
Delayed removal of eradicable infection source (>2 days)[a]	3/7 (42.9)	1/1 (50.0)	>0.99	2/4 (50.0)	0/0	NC
Inadequate initial antifungal therapy	52 (51.0)	23 (48.9)	0.82	18 (38.3)	12 (27.9)	0.37
Inadequate definitive antifungal therapy	13 (12.7)	6 (12.8)	>0.99	3 (6.4)	6 (14.0)	0.30
Initial echinocandin therapy	17 (16.7)	12 (25.5)	0.20	12 (25.5)	8 (18.6)	0.43

CCI, Charlson Comorbidity Index; IQR, interquartile range; ICU, intensive care unit; ANC, absolute neutrophil count; CVC, central venous catheter; NC, not calculated.

Data are presented as no. (%) of patients, unless otherwise indicated.

[a] Percentage of patients with eradicable infection source.

was the only risk factor for 30-day mortality in those patients (Table III). Neither the adequacy of initial antifungal therapy nor that of definitive antifungal therapy was associated with 30-day mortality, irrespective of the severity of comorbidities. When the analysis of risk factors associated with 30-day mortality according to the severity of comorbidities was performed, the results for patients with catheter-related candidaemia were not significantly different from those for all patients with candidaemia. In addition, when the risk factors of 30-day mortality for candidaemia according to the severity of comorbidities were analysed with various cut-off values for CCI score, the results in patients with low CCI scores were comparable with a cut-off value of CCI score of 1–3 and the results in patients with high CCI scores were comparable with a cut-off value of CCI score of 4–6 (data not shown).

Impact of delayed CVC removal by severity of comorbidities

To verify the impact of delayed CVC removal, 182 patients with candidaemia in whom CVCs had been placed were analysed. One hundred and fifty-four (84.6%) patients underwent CVC removal: Of 182 patients with candidemia in whom CVCs had been placed, 154 (84.6%) underwent CVC removal; 88 (48.4%) had early CVC removal and 94 (51.6%) included in delayed CVC removal group [66 (36.2%) underwent delayed CVC removal and 28 (15.4%) did not undergo CVC removal. Gender, age, underlying diseases and *Candida* spp. distribution were comparable between the early and delayed CVC removal groups, irrespective of the CCI score (low or high). Definite CVC-related candidaemia was more common in patients who underwent early CVC removal with low CCI scores [70.3% (45/64) vs 43.5% (20/46); *P*=0.01]. Septic shock tended to be more common in the delayed CVC removal group than in the early CVC removal group, irrespective of CCI score (low or high), although statistical significance was not attained [low CCI score group, 43.5% (20/46) vs 29.7% (19/64); *P*=0.14; high CCI score group, 45.8% (22/48) vs 25.0% (6/24); *P*=0.09].

Delayed CVC removal (>2 days after onset of candidaemia) was associated with increased 30-day mortality in patients with low CCI scores (50.0% vs 20.3%; *P*=0.001), but not in those with high CCI scores (50.0% vs 47.9%; *P*=0.87; Figure 1). Similar results were shown in CVC-related candidaemia and non-CVC-related candidaemia (Figure 1). Kaplan–Meier estimates showed that delayed CVC removal was associated with poorer survival than early CVC removal in patients with low CCI scores, but not in patients with high CCI scores (Figure 2). On subgroup analysis of patients with low CCI scores, delayed CVC removal remained associated with increased 30-day mortality in patients with septic shock [80.0% (16/20) vs 42.1% (8/19); *P*=0.02], but no such association was apparent in patients without septic shock [26.9% (7/26) vs 11.1% (5/45); *P*=0.11]. These results did not change on subgroup analysis of patients with CVC-related candidaemia alone (data not shown).

Discussion

Delayed CVC removal was found to increase 30-day mortality in patients with candidaemia and low CCI scores, especially those with septic shock. However, early CVC removal did not affect the 30-day mortality rate in those with high CCI scores. Septic shock was the only risk factor for 30-day

Table III

Multi-variate analysis of risk factors for 30-day mortality in patients with candidaemia according to the severity of comorbidities

CCI group	Characteristic	OR (95% CI)	*P*
Low CCI (score ≤3)	Septic shock	9.54 (3.28–27.73)	<0.001
	Delayed CVC removal (>2 days)	4.73 (1.68–13.30)	0.003
	Candida parapsilosis infection	0.15 (0.03–0.84)	0.03
	Cerebrovascular disease	0.28 (0.10–0.82)	0.02
High CCI (score ≥4)	Septic shock	13.04 (3.82–44.45)	<0.001

CCI, Charlson Comorbidity Index; OR, odds ratio; CI, confidence interval; CVC, central venous catheter.

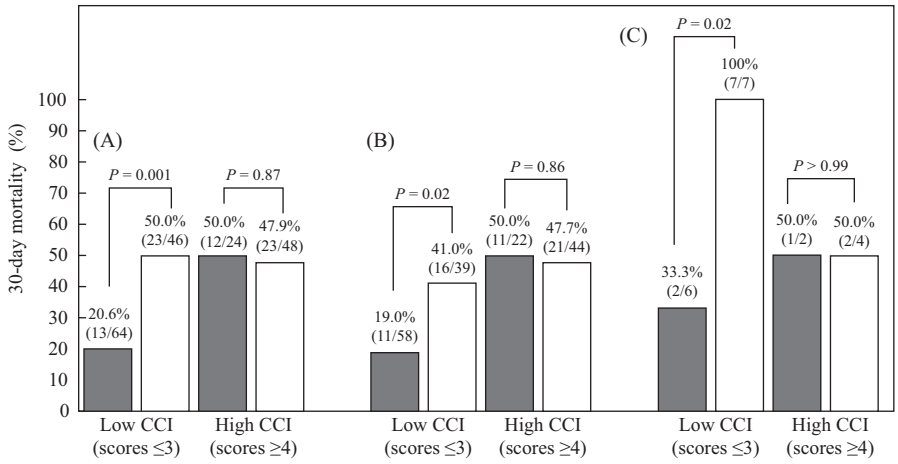

Figure 1. Effect of delayed removal of central venous catheter on 30-day mortality according to the severity of comorbidities in patients with candidaemia and central venous catheter placement (A), which was stratified by central venous catheter (CVC)-related candidaemia (B) and non-CVC-related candidaemia (C). CCI, Charlson Comorbidity Index. Grey bars, early CVC removal (≤2 days of onset of candidaemia); white bars, delayed CVC removal (>2 days of onset of candidaemia).

mortality in the latter group of patients. Neither inappropriate initial nor inappropriate definitive antifungal therapy affected the mortality rate, irrespective of the severity of comorbidities.

CVC removal has been recommended due to a beneficial effect with regard to enhanced survival in candidaemia [10–13]. However, CVCs are often essential for the management of such patients, especially those who are severely ill. These patients require intensive monitoring and regular administration of therapeutic agents [21]. If a CVC is removed early, re-insertion may be required, which is associated with possible complications, including pneumothorax, bleeding, and insertion failure attributable to poor venous access [22]. Thus, physicians are usually reluctant to remove CVCs immediately without sufficient evidence that candidaemia dictates early CVC removal. However, the effect of prompt CVC removal from patients with candidaemia remains controversial. Garnacho-Montero *et al.* found that early CVC removal (≤48 h) decreased the mortality of patients with primary candidaemia and a CVC in place, but not that of patients with secondary non-catheter-related candidaemia [17]. Raad *et al.* noted that early CVC removal (≤72 h) significantly improved the response to catheter-related candidaemia in patients with cancer [23]. Liu *et al.* found significantly better survival of patients with cancer and candidaemia undergoing early CVC removal (≤72 h) compared with patients undergoing delayed CVC removal, even when patients were stratified by severity of illness and Eastern Cooperative Oncology Group performance status [11].

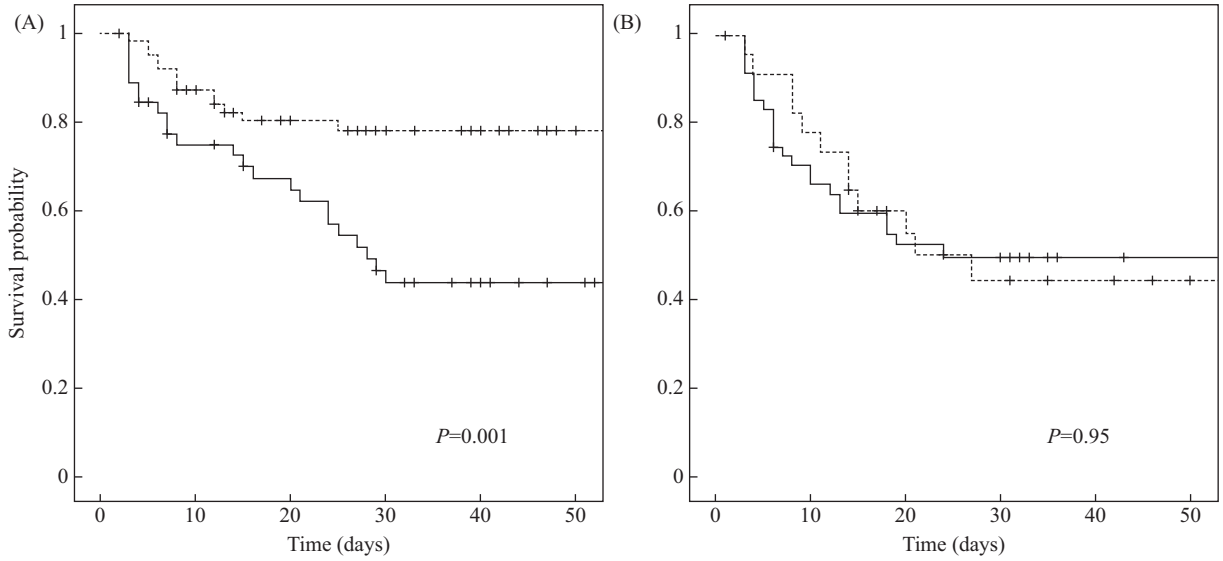

Figure 2. Kaplan–Meier survival curves after candidaemia for (A) patients who had low Charlson Comorbidity Index scores (≤3) with early removal of central venous catheter (CVC) (*N*=64, dashed line) vs patients with delayed CVC removal (*N*=46, solid line) (*P*=0.001, log-rank test) and (B) those who had high Charlson Comorbidity Index scores (≥4) with early CVC removal (*N*=24, dashed line) vs patients with delayed CVC removal (*N*=48, solid line) (*P*=0.95, log-rank test).

However, the subgroups were too small to allow evaluation of the impact of delayed CVC removal, and the analysis was not adjusted for the adequacy of antifungal therapy. On the contrary, Rodriguez *et al*. found no benefit of CVC removal on day 0 or 1 following the development of candidaemia (catheter-related or not) [18]. On subgroup analysis, early CVC removal did not reduce the mortality of ICU patients or those with malignancies. However, the information about the proportion of patients with neutropenia seemed insufficient in that study. A large multi-centre prospective trial failed to show any beneficial effect of early CVC removal (≤48 h) in terms of the rate of persistent candidaemia or survival [24]. These discrepant results suggest that certain patients with candidaemia might benefit from early CVC removal.

Notably, this study found that the severity of comorbidities affected the impact of delayed CVC removal on mortality. Previous studies have shown the implications of delayed CVC removal on outcomes depending on the severity of illness, malignancy, performance status and prior history of surgery, but not on the severity of comorbidities in patients with candidaemia [11,18]. Patients with malignancies can have low or high CCI scores because malignancies are diverse, including haematological malignancies, non-metastatic solid cancers (which have good prognosis) and metastatic solid cancers. Therefore, malignancy *per se* does not reflect the severity of underlying disease. This study found that the beneficial effect of early CVC removal on mortality was confined to patients with candidaemia and low CCI scores. This association was observed in patients with CVC-related and non-CVC-related candidaemia. The cases of unknown origin of infection, which accounted for 68% of non-CVC-related candidaemia, may be related to CVC-related infection. Therefore, this may influence the consistent result in patients with non-CVC-related candidaemia in comparison with those with CVC-related candidaemia. Velasco *et al*. reported that although no difference in mortality was evident between patients undergoing early (≤72 h) and delayed CVC removal, a survival benefit of early CVC removal was evident for patients with Karnofsky performance score >60 on stratified analysis [25]. This result may be in line with the present findings; patients with low CCI scores tend to exhibit better Karnofsky performance status. The beneficial effect of early CVC removal in patients with candidaemia was particularly apparent in those with septic shock. One previous study highlighted the importance of timely source control (within 24 h) to reduce the mortality of patients with candidaemia-caused septic shock [4]. Hence, CVCs should be removed promptly from patients with septic shock. However, the present study found no clear effect of early CVC removal on the survival of patients with candidaemia and high CCI scores. Septic shock was the only risk factor for 30-day mortality in such patients. Host factors and the severity of underlying diseases have greater impacts on mortality than the timing of CVC removal in patients with high CCI scores. The data indicate that patients with severe comorbidities may not recover from septic shock, despite early CVC removal or adequate antifungal therapy. Andes *et al*. found that CVC removal was beneficial for patients in lower Acute Physiology and Chronic Health Evaluation (APACHE) II quartiles, but that neither CVC removal nor the type of antifungal therapy prescribed affected the outcomes of patients in the highest APACHE II quartile [12]. Therefore, it is essential to focus on prevention of catheter-related candidaemia by emphasizing hand hygiene, use of maximal sterile barrier precautions, removal of unnecessary CVCs as soon as possible, and education, especially in patients with high CCI scores.

This study identified risk factors for 30-day mortality from candidaemia in terms of the severity of comorbidities. Septic shock was a risk factor for 30-day mortality of patients with low and high CCI scores, in line with previous findings [4,26,27]. Bloodstream infections with *C. parapsilosis* were associated with decreased mortality in patients with low CCI scores, in line with the results of previous studies [12,18], perhaps reflecting a lower rate of septic shock and a higher rate of definite CVC-related candidaemia in those infected with *C. parapsilosis* compared with patients infected with other *Candida* spp. The present study found that the adequacy of antifungal therapy did not affect mortality. Relevant findings from earlier works differ. Some showed that delayed administration of antifungal therapy or inadequate dosing with antifungal agents increased mortality from candidaemia [2,10,28]. However, other works failed to find such associations in either primary or secondary candidaemia [17,18]. Further studies are required to clarify the impact of inadequate antifungal therapy on mortality in patients with candidaemia.

This study has certain limitations. First, the study was retrospective in nature, and the management of candidaemia was at the discretion of the attending physicians. Second, only a small number of neutropenic patients were included; as such, it was not possible to show whether early CVC removal is protective in such patients. Third, no cases of bloodstream infection caused by *C. krusei* were encountered; this species exhibits reduced susceptibility to fluconazole. The timing of CVC removal from patients with candidaemia was found to reduce the mortality of patients with less serious comorbidities. Despite these limitations, this study may explain the inconsistency of previous data on the relationship between early CVC removal and mortality in patients with candidaemia.

In conclusion, early CVC removal from candidaemia improves the survival of those with low CCI scores, especially patients with septic shock. However, the timing of CVC removal may not affect the outcomes of patients with high CCI scores. The timing of CVC removal from patients with candidaemia may be chosen by reference to the severity of their underlying diseases.

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