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## Acute Clostridioides difficile Infection in Hospitalized Persons Aged 75 and Older: 30-Day Prognosis and Risk Factors for Mortality

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### ► To cite this version:

Arnaud Caupenne, Pierre Ingrand, Isabelle Ingrand, Emmanuel Forestier, Claire Roubaud-Baudron, et al.. Acute Clostridioides difficile Infection in Hospitalized Persons Aged 75 and Older: 30-Day Prognosis and Risk Factors for Mortality. Journal of the American Medical Directors Association, 2020, 21 (1), pp.110 - 114. 10.1016/j.jamda.2019.07.002 . hal-03489068

HAL Id: hal-03489068

<https://hal.science/hal-03489068>

Submitted on 21 Jul 2022

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**Title:** Acute *Clostridioides difficile* infection in hospitalized persons aged 75 and older: 30-day prognosis and risk factors for mortality.

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**Running title:** *Clostridioides difficile* infection in the elderly

**Key words:** elderly, *Clostridioides difficile*, infection, prognosis, recurrence, mortality

**Funding sources:** This work was supported by Astellas Pharmaceuticals Europe (Grant 10000€).

**Word, reference, and graphics count:** 1944 words, 36 references, 2 graphics and 2 tables

### **Brief summary**

Clostridioides difficile infection in the elderly was associated with a 30-day mortality of 12.6%. Comorbid illness and new heart, lung, or kidney failure predicted a poor prognosis.

**Acknowledgments:** Maulin MD, Puigserver MD (Aix); Fraisse MD (Alès); Pignon MD, Tremblay Nguyen MD (Angers); Jarry MD (Angoulême), Piet MD (Annecy); Bard MD (Belley); Geffroy MD, Friocourt MD (Blois); Bourdel-Marchasson MD PHD, Dubos MD, Roubaud MD, PhD (Bordeaux); Dardalhon MD, Forestier MD (Chambery); Ghazali MD (Châtelleraut); Hauler MD (Colmar); Dadet MD (Clermont-Ferrand); Suel MD (Dieppe); Piroth MD PhD, Putot MD (Dijon); Berode MD (Dunkerque); Dascalita MD (St Etienne); Carriere MD (St Galmier); Gavazzi MD PhD, Pavese MD (Grenoble); Derrien MD (Landerneau); Albrand MD, Chala-Hayet MD, Federico MD, Gaujard MD, Martin-Gaujard MD (Lyon); Jeandel MD PhD, Terminet MD (Montpellier); Arlaud MD, Turpin MD (Nice); Viala MD, de Wazières MD PhD (Nîmes); Kahlifa MD (Niort); Bourgeois MD (Orléans); Breining MD, Durand-Gasselin MD, Greffe MD, Moulias MD, Rouveix MD PhD (Paris); Eden MD, Silga MD (Perpignan); Aribi MD (Plaisir); Chartier MD (Rochefort); Guignery-Kadri MD, Kloul MD, Renaudier MD (Rouen); Bernard MD PhD, Lamande MD (Tours); Marechal MD, Pietropaoli MD (Trevoux); Fevrier MD, Decours MD, Guimard MD, Martin MD, Morier MD, Pelerin MD (Hôpital de Vendée); Jestin MD (St Yvi).

## 1 **Abstract**

2 *Objectives:* To assess the 30-day mortality predictive markers in the oldest patients with  
3 *Clostridioides difficile* infection (CDI) and to analyze the accuracy of the European severity  
4 risk markers in this population.

5 *Design:* Observational prospective multicenter cohort study conducted by the French  
6 Infectious Diseases Society and Geriatrics Society networks. An electronic questionnaire was  
7 sent to the members of both societies regarding their participation. Each investigator used an  
8 online survey to gather the data.

9 *Setting and Participants:* Patients aged  $\geq 75$  years hospitalized in French geriatric or  
10 infectious wards with confirmed diagnosis of CDI between March 1, 2016 and May 1, 2017.

11 *Methods:* Clinical and laboratory parameters included medical history and comorbidities with  
12 the Cumulative Illness Rating Scale (CIRS). Criteria increasing the risk of severe disease  
13 were recorded as listed in the European guidelines. Therapeutic management, recurrence and  
14 mortality rates were assessed at day 30 after diagnosis.

15 *Results:* Included patients numbered 247; mean age was 87.2 (SD 5.4). Most of the CDI  
16 incidences (66.4%) were health-care associated infections with 81% diagnosed within 30 days  
17 of hospitalization; CIRS mean score was 16.6 (SD 6.6). Markers of severity  $\geq 3$  included 97  
18 patients (39.3%). Metronidazole was the main initial treatment (51.0%). *Clostridioides*  
19 *difficile* infection in the elderly was associated with a 30-day mortality of 12.6%. Multivariate  
20 analysis showed that baseline CIRS score (HR 1.06 per one-point increase, 95% CI 1.00-1.12)  
21 and evidence of cardiac, respiratory, or renal decompensation (HR 3.04, 95% CI 1.40-6.59)  
22 were significantly associated with mortality.

23 *Conclusions and implications:* European severity markers are adequate in the oldest old.  
24 Organ failure and comorbidities appeared to be the main markers of prognosis, and these  
25 should raise the awareness of practitioners. Although antibiotic treatment was not predictive  
26 of mortality, our results point out the lack of adherence to current guidelines in this  
27 population.

## 28 **Introduction**

29 *Clostridium difficile*, recently reclassified as *Clostridioides difficile*, represents the most  
30 common pathogen cause of health care associated diarrhea in developed countries.<sup>1,2</sup> Over the  
31 past ten years, there has been an important increase in both incidence and severity of CD  
32 infection (CDI).<sup>3</sup> In a national study conducted in 2009, the incidence in France was estimated  
33 as up to 2.28 cases/10,000 patient-days in acute care and 1.14 cases/10,000 patient-days in  
34 rehabilitation and long-term care.<sup>4</sup> The risk of recurrence is estimated between 10 and 30%<sup>5-7</sup>  
35 and all-cause CDI-related mortality ranges from 4.5% to 33.2%.<sup>8-12</sup> European guideline  
36 documents based on several studies report that elderly patients are at increased risk of  
37 recurrence and mortality.<sup>13</sup> Patients aged 65 and older represent 60% to 70% of CDI cases.<sup>14-</sup>  
38 <sup>16</sup> This age group is vulnerable because of more frequent and prolonged hospitalizations,  
39 senescence of immune mechanisms and altered intestinal microbiota.<sup>17-19</sup> Still, few studies  
40 focused on patients over 75 years of age<sup>10,20-22</sup> and predictive markers for short-term mortality  
41 in this population are scarcely described.<sup>8,23,24</sup> We set up a national survey, named CLOdi, to  
42 assess the 30-day mortality predictive markers in the oldest patients and to analyze the  
43 accuracy of the European severity risk markers in this population.

44

45

## 46 **Methods**

47 CLOdi is a French observational prospective survey that included patients aged 75 years and  
48 over with diagnosis of CDI, hospitalized in geriatric and infectious wards between March 1,  
49 2016 and May 1, 2017.

### 50 *Data collection*

51 The study was conducted by the French Infectious Diseases Society and Geriatrics  
52 Society networks (*Société de Pathologies Infectieuses de Langue Française and Société*  
53 *Française de Gériatrie et de Gériatrie*) and approved by the French regulatory  
54 authorities, the *Comité Consultatif sur le Traitement de l'Information en matière de Recherche*  
55 *dans le domaine de la Santé* (CCTIRS) (Consultative committee on information-processing in  
56 health research) in September 2015, and the *Commission Nationale Informatique et Libertés*  
57 (CNIL) (Commission for protection of private data) in December 2015.

58 An electronic questionnaire was sent to the members of both societies regarding their  
59 participation on a voluntary basis. Each investigator who agreed to participate used an online  
60 survey to include patients at diagnosis, filled in the data during the course of CDI, and  
61 assessed case evolution 30 days after CDI diagnosis. The diagnosis of CDI was based on  
62 clinical symptoms and positivity of both CDI laboratory tests (glutamate dehydrogenase and  
63 toxins A or B) in stool samples. Health-care associated CDI was defined when infection  
64 occurred 48 hours or more after index hospitalization. When CDI was the cause of  
65 hospitalization or occurred within 48 hours of hospitalization, it was considered as  
66 community-acquired. The clinical and laboratory parameters were collected, as well as the  
67 markers of risk of severity and the CDI antibiotic sequences. The European markers of risk of  
68 severity are as follows: age  $\geq$  65 years, leukocyte count  $>$  15 000/mm<sup>3</sup>, rise in serum

69 creatinine level  $\geq$  50% of the premorbid level and blood albumin  $<$  30g/L and severe  
70 underlying disease.<sup>13</sup> Comorbidities were evaluated at admission by the Cumulative Illness  
71 Rating Scale (CIRS).<sup>25,26</sup> Total CIRS score was recorded at the onset of CDI. We decided to  
72 use the median score to define comorbidity as severe. Organ failure was arbitrarily assessed  
73 during the course of CDI, relying either on intravenous use of loop diuretics for cardiac  
74 insufficiency, and/or need for oxygen, and/or rise in serum creatinine level  $\geq$  50% of the  
75 premorbid level, for renal decompensation, according to the European guidelines  
76 documents.<sup>13</sup>  
77 Treatment and outcome (length of hospital stay, recurrence of CDI, mortality) were recorded.  
78 Recurrence was defined as new CDI confirmed after the onset of a previous episode, provided  
79 the symptoms from the previous episode resolved for at least 48 hours after completion of  
80 initial treatment.

81

## 82 *Data analysis*

83 Descriptive statistics were expressed as mean  $\pm$  standard deviation (SD) for continuous  
84 variables or absolute number and percentage for categorical variables. Unadjusted hazard  
85 ratios (HR) and 95% confidence intervals (CI) were calculated from univariate Cox regression  
86 analysis. Adjusted HRs were calculated for significant variables ( $P < .05$ ) from multivariate  
87 Cox analysis performed by stepwise elimination from an initial model including variables  
88 with univariate  $P < .25$ . The proportional risk assumption has been assessed. Analyses were  
89 performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

## 90 **Results**

### 91 *Baseline characteristics*

92 Investigators (63) included 247 hospitalized patients (mean age 87.2, SD 5.4, range 75-99)  
93 from 34 hospitals during the 14-month study period (Table 1); 31 (12.6%) patients came from  
94 nursing homes; CDI was diagnosed during an acute care or rehabilitation hospitalization; 195  
95 (78.9%) patients were hospitalized in acute care hospitals and 52 (21.1%) in rehabilitation  
96 hospitals; CDI was community-acquired, including residents of nursing homes, in almost a  
97 third of patients. Main reasons for hospitalization were an infectious disease (27.1%), diarrhea  
98 (24.6%), and asthenia (8.5%). A past history of CDI was reported in 33 patients (13.4%).  
99 CDI diagnosis had occurred within 30 days following admission in 199 (81%) cases and  
100 within 90 days in 240 (98%) cases; 106 patients (42.9%) had antibiotic exposure at the time of  
101 CDI, mainly betalactamins (89%), which were discontinued in 68 cases (64.1%). Baseline  
102 CIRS mean score was 16.6 (SD 6.6, range 2-34, median 14) and 80 (32.4%) patients were  
103 classified with severe comorbidity (CIRS score > 14). Mean CIRS score was 14.4 (SD 6.5) in  
104 patients diagnosed and treated in a rehabilitation hospital and 12.2 (SD 6.4) in patients  
105 diagnosed and treated in an acute care hospital ( $P = .023$ ). Sixty-two (25.1%) patients  
106 presented with either use of loop diuretics and/or rise in serum creatinine level  $\geq 1.5$  times the  
107 premorbid level and/or need for oxygen at the time of CDI, but none was admitted to  
108 intensive care. Ninety-seven (39.3%) had  $\geq 3$  severity risk markers. Metronidazole was the  
109 most common initial treatment (51.0%), administered intravenously in 16 patients (12.7%).  
110 Thirty-six (14.6%) patients had a second line treatment with fidaxomicin (52.8%),  
111 vancomycin (41.7%) and metronidazole (the last in two cases).

112

### 113 *Course of infection*

114

115 Median length of hospitalization was 26 days (range 5-254) with 89 patients (36%) staying  
116 over 30 days. Ten patients died before 10 days of treatment. At day 30 after CDI diagnosis,



117 mortality rate was 12.6% with 58.1% of these patients dying during CDI treatment; Mortality  
118 rate at day 30 was similar in acute care hospitals and rehabilitation hospitals ( $P = .27$ ). One  
119 patient died before prescription of any CDI treatment; 38 patients did not have discontinuation  
120 of the likely offending antibiotic at the onset of CDI, with mortality rate of 28.9% at day 30  
121 (11/38).

122 Recurrence rate at day 30 was 13%. When recurrence occurred, treatment was the same as the  
123 one for the first episode in 9 cases (28.1%), vancomycin was prescribed in 10 cases (31.2%),  
124 fidaxomicin in 7 cases (21.9%) and metronidazole in one case. Three patients (9.4%) were  
125 treated with combination of antibiotics and two did not have any therapeutic management.  
126 Among the 31 deaths at day 30, 9 (29%) patients had presented with a recurrence.

127 Univariate analysis showed that occurrence of organ failure, CIRS score, severe comorbidity  
128 (CIRS > 14) and a higher number of severity risk markers ( $\geq 3$ ) were significantly associated  
129 with mortality (Table 2). Multivariate analysis showed that CIRS score (HR 1.06 per one-  
130 point increase, 95% CI 1.00-1.12) and occurrence of organ failure as defined (HR 3.04, 95%  
131 CI 1.40-6.59) were significantly associated with mortality at day 30 (Table 2, Figures 1 and  
132 2). Thus an increase of 10 points of the CIRS score would increase the risk of mortality up to  
133 78%.

134

## 135 **Discussion**

136 CDI is known as a severe disease, but data in the oldest old are scarce. Our study reports  
137 management and short-term prognosis in 247 patients, hospitalized in geriatrics and infectious  
138 diseases wards with a mean age of 87.2 (SD 5.4) years. We wanted to focus the analysis  
139 within the 30-day interval after CDI diagnosis to better consider the weight of the infection at  
140 short term. Our results show a rate of 12.6% of all-cause mortality at day 30, 58.1% occurring  
141 during CDI episode treatment. The rate of mortality was the same in acute care hospitals and

142 in rehabilitation hospitals. Important to note that in France, rehabilitation centers are  
143 considered as rehabilitation hospitals and a patient with CDI in a rehabilitation hospital is  
144 treated in the rehabilitation hospital. This rate is lower than 30-day mortality rates reported in  
145 literature, which were between 16.5% and 32.2% in patients aged over 65 and 80.<sup>21,27,28</sup>

146 Organ failure defined as, relying on intravenous loop diuretics, and/or need for oxygen, and/or  
147 rise in serum creatinine level  $\geq 50\%$  of the premorbid level was the most predictive parameter  
148 of short-term mortality (HR 3.04, CI 95% 1.40-6.59). Among these criteria, renal failure  
149 occurring during the course of CDI illness and relying on rise in serum creatinine level  $\geq 1.5$   
150 times the premorbid level was the most relevant (Table 2). These results underline the  
151 predictivity of a vulnerable status. Indeed, our results highlight the weight of comorbidities in  
152 this very old population having a CIRS score significantly associated with mortality ( $P =$   
153  $.033$ ). Other studies conducted in similar aged populations focused on mortality risk  
154 factors,<sup>22,29-32</sup> but none of them had assessed comorbidities with CIRS.<sup>22,30-32</sup> We used the  
155 criteria “CIRS score  $> 14$ ” to define the comorbidity as severe (figure 2). Our results show  
156 that this criterion was significantly associated ( $P = .013$ ) with mortality in univariate analysis.  
157 It confirms the central place of the CIRS score in CDI mortality prognosis in the elderly.  
158 Despite its significance, we could not logically insert this median score in multivariate  
159 analysis with the CIRS continuous variable.

160 The adequacy of European markers of the risk of severity with mortality, including  
161 comorbidities, were already reported on in previous meta-analysis and retrospective  
162 studies.<sup>7,29</sup> Our results also showed that patients with  $\geq 3$  markers of risk of severity had a  
163 higher risk of mortality ( $P = .022$ ).

164 Almost half of deaths (48.4%) occurred before 10 days of therapeutic management, verifying  
165 the weight of organ failure and questioning the adequacy of the initial antibiotic. Although  
166 antibiotic prescription was not associated with mortality at day 30, metronidazole was the

167 most frequent initial treatment (51.0%), as reported in the literature.<sup>16,33</sup> Vancomycin and  
168 fidaxomicin were more frequently prescribed as a second-line treatment and upon recurrence.  
169 This highlights the lack of adherence to the guidelines, which do not recommend prescription  
170 of metronidazole for patients profiled with disease severity markers.<sup>13,34</sup> Fidaxomicin  
171 represents a small part of the CDI initial treatment.<sup>33</sup> This molecule is recent, with a higher  
172 cost, which may be a barrier in clinical practice despite the lower risk of recurrence associated  
173 with this treatment.<sup>35-36</sup>

174 However, due to the weight of comorbidity and risk of organ failure in CDI short-term  
175 prognoses, our results enhance the need to better control modifiable risk factors of CDI, such  
176 as antibiotics prescription and hygiene control.

177 On the one hand, the practices that we observe adhere to European and US guidelines for  
178 diagnosis of CDI, as all patients had both clinical symptoms and positive laboratory tests. On  
179 the other hand, the practices deviate from treatment guidelines, as patients > 65 years old with  
180 CDI should not be treated with metronidazole.<sup>13,34</sup>

181 Our study has some limitations. First, it is a survey. All elderly patients with CDI may not  
182 have been included by investigators during the study period. Second, a longer follow-up  
183 should be also performed to assess markers associated with recurrences and the real impact of  
184 CDI antibiotic treatment.

## 185 **Conclusions and Implications**

186 This prospective survey, in hospitalized patients aged over 75 with CDI, confirms the high  
187 risk of short-term mortality in the elderly, with over half of deaths occurring before the end of  
188 therapeutic management. European severity markers are adequate in the oldest old. Organ  
189 failure, mainly renal failure, and comorbidities appeared to be the main markers of prognosis.  
190 These markers should raise awareness of practitioners to anticipate prognosis of this infection.

191 Although antibiotic treatment was not predictive of short term mortality, our results point out  
192 the lack of adherence to current guidelines in this vulnerable population.

193

#### 194 **Conflicts of interest**

195 We declare that none of the authors have any conflicts of interest.

196

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## 291 **Figure Legends**

292 Fig.1.

293 Kaplan-Meyer Plot of 30-day survival probability after *Clostridioides difficile* infection  
294 diagnosis comparing patients with or without organ failure.

295 Organ failure was assessed when use of diuretics or rise in serum creatinine level  $\geq 1.5$  times  
296 the premorbid level, or need for oxygen.

297 Fig.2.



- 298 Kaplan-Meyer Plot of 30-day survival probability after *Clostridioides difficile* infection
- 299 diagnosis according to Cumulative Illness Rating Scale (CIRS) score (cut-off of 14).

**Table 1**Characteristics of patients with *Clostridioides difficile* infection.

Variable	Population (N = 247)
Women n (%)	162 (65.6)
Mean age (years), (SD)	87.2 (5.4)
Men	86.8 (5.4)
Women	87.4 (5.4)
Abode	
Community-dwelling (%)	216 (87.4)
Nursing home (%)	31 (12.6)
Baseline CIRS score, mean (SD)	12.6 (6.6)
Number of medications, mean (SD)	7.4 (3.5)
PPI, n (%)	129 (52.2)
Antibiotic therapy at diagnosis (%)	109 (44.1)
Penicillin (%)	61 (56.0)
Cephalosporin (%)	36 (33.0)
Health-care associated CDI, n (%)	164 (66.4)
Organ failure during the course of CDI*, n (%)	62 (25.1)
- Use of intravenous loop diuretics (%)	29 (46.8)
- Renal failure (%)	53 (85.5)
- Respiratory failure (%)	15 (24.2)
Mean duration of isolation precaution (days) (range)	10 (2-82)
First line treatment, n (%)	
- Metronidazole (%)	126 (51)
- Vancomycin (%)	91 (36.9)
- Fidaxomicin (%)	25 (10.1)
Combination of antibiotics (%)	4 (1.6)
Median duration of antibiotic therapy (days), (range)	10 (1-40)
Severity risk markers ( $\geq 3$ ), n (%)	97 (39.3)
- Age ( $> 65$ years)	247 (100)
- Leukocyte count $> 15\ 000/\text{mm}^3$	72 (29.1)
- Rise in serum creatinine level <sup>†</sup>	53 (21.5)
- Blood albumin $< 30\text{g/L}$	130 (52.6)
Severe comorbidity <sup>‡</sup>	182 (73.7)

CIRS: Cumulative Illness Rating Scale; PPI: proton pump inhibitors; CDI: *Clostridioides difficile* infection  
Severity risk markers were assessed according to the European [guideline](#) documents.<sup>13</sup>

\*Organ failure was assessed when use of intra-venous loop diuretics or rise in serum creatinine level  $\geq 1.5$  times the premorbid level or need for oxygen.

<sup>†</sup>Rise in serum creatinine level  $\geq 1.5$  times the premorbid level.

<sup>‡</sup>Severe comorbidity (CIRS score  $> 14$ ).

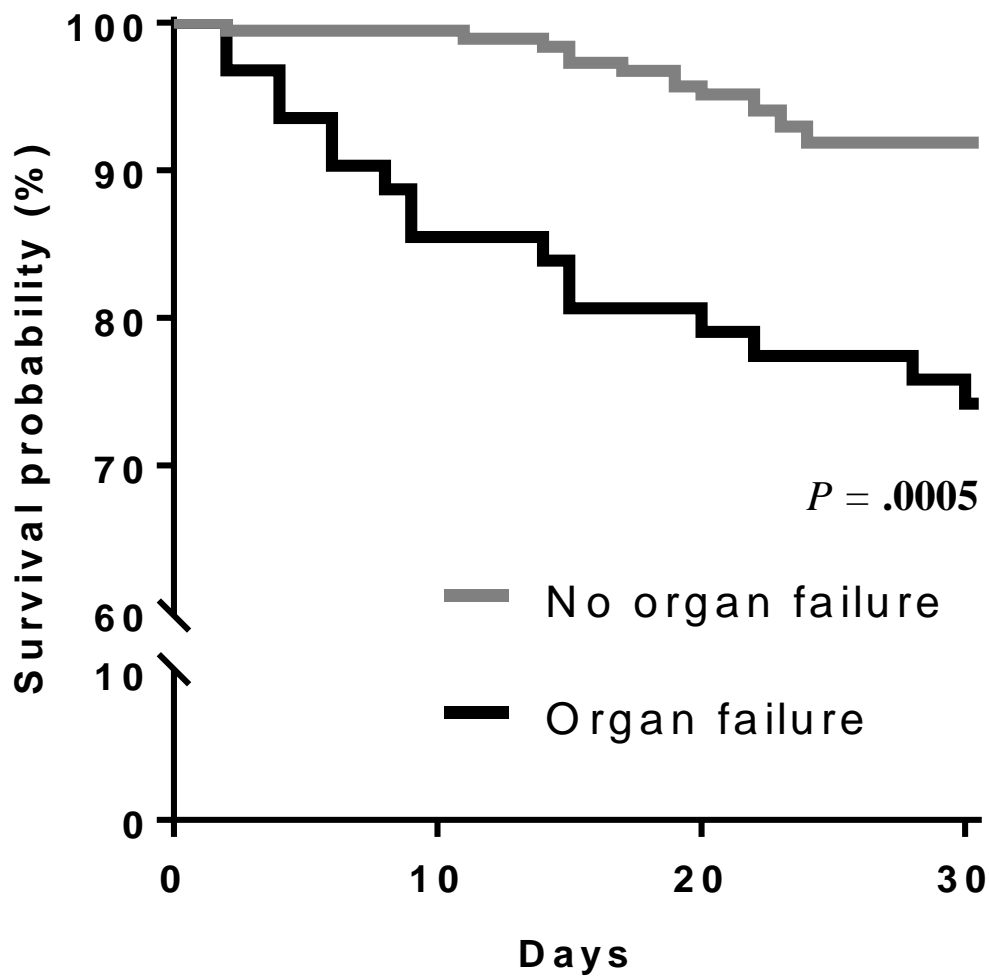
**Table 2**Risk factors for mortality at day-30, in patients with *Clostridioides difficile* infection.

Variables	Alive patients (N = 216)	Dead patients (N = 31)	Univariate analysis		Multivariate analysis	
			P Value	Hazard Ratio	P Value	Hazard Ratio
Women, n (%)	145 (67.1)	17 (54.8)	.19	1.62 [0.78 – 3.27]	-	
Age (years), mean (SD)*	87.0 (5.4)	88.8 (4.9)	.088	1.06 [0.99 – 1.13]	-	
Antibiotic therapy in previous 3 months n (%)	130 (60.2)	13 (41.9)	.061	1.97 [0.97 – 4.10]	-	
Number of medications mean (SD)*	7.3 (3.6)	8.1 (3.5)	.25	1.06 [0.96 – 1.16]	-	
Non-CDI antibiotic therapy at time of diagnosis, n (%)	91 (42.1)	18 (58)	.090	1.84 [0.90 – 3.76]	-	
Health-care associated CDI, n (%)	141 (65.3)	23 (74.2)	.21	1.67 [0.75 – 4.22]	-	
CIRS, mean (SD)*	12.1 (6.3)	16.0 (6.9)	<b>.0037</b>	1.08 [1.03 – 1.14]	<b>.033</b>	1.06 [1.00 – 1.12]
Organ failures during the course of CDI**, n (%)	46 (21.3)	16 (51.6)	<b>.0005</b>	3.64 [1.80–7.36]	<b>.0048</b>	3.04 [1.40 – 6.59]
Treatments during the course of infection, n (%)						
Metronidazole	116 (53.7)	15 (48.4)	.54	0.80 [0.39 – 1.63]	-	
Vancomycin	95 (43.9)	14 (45.2)	.89	1.05 [0.51 – 2.13]	-	
Fidaxomicin	44 (20.4)	5 (16.1)	.56	0.76 [0.26 – 1.82]	-	
Severity risk markers, n (%)						
≥ 3 markers	77 (35.6)	20 (64.5)	<b>.0028</b>	3.07 [1.50 – 6.62]	-	
Age (> 65 yrs)	216 (100)	31 (100)	-		-	
Leukocyte count > 15,000/mm <sup>3</sup>	61 (28.2)	11 (35.5)	.39	1.39 [0.64 – 2.84]	-	
Rise in serum creatinine level <sup>+</sup>	42 (19.4)	11 (35.5)	<b>.048</b>	2.18 [1.01 – 4.46]	-	
Blood albumin < 30 g/l	110 (50.9)	20 (64.5)	.15	1.71 [0.83 – 3.69]	-	
Severe comorbidity <sup>±</sup>	64 (29.6)	16 (51.6)	<b>.013</b>	2.50 [1.22 – 5.21]	-	

CDI: *Clostridioides difficile* infection; CIRS: Cumulative Illness Rating Scale;Severity risk markers were assessed according to the European guideline documents.<sup>13</sup>

\*per unit change

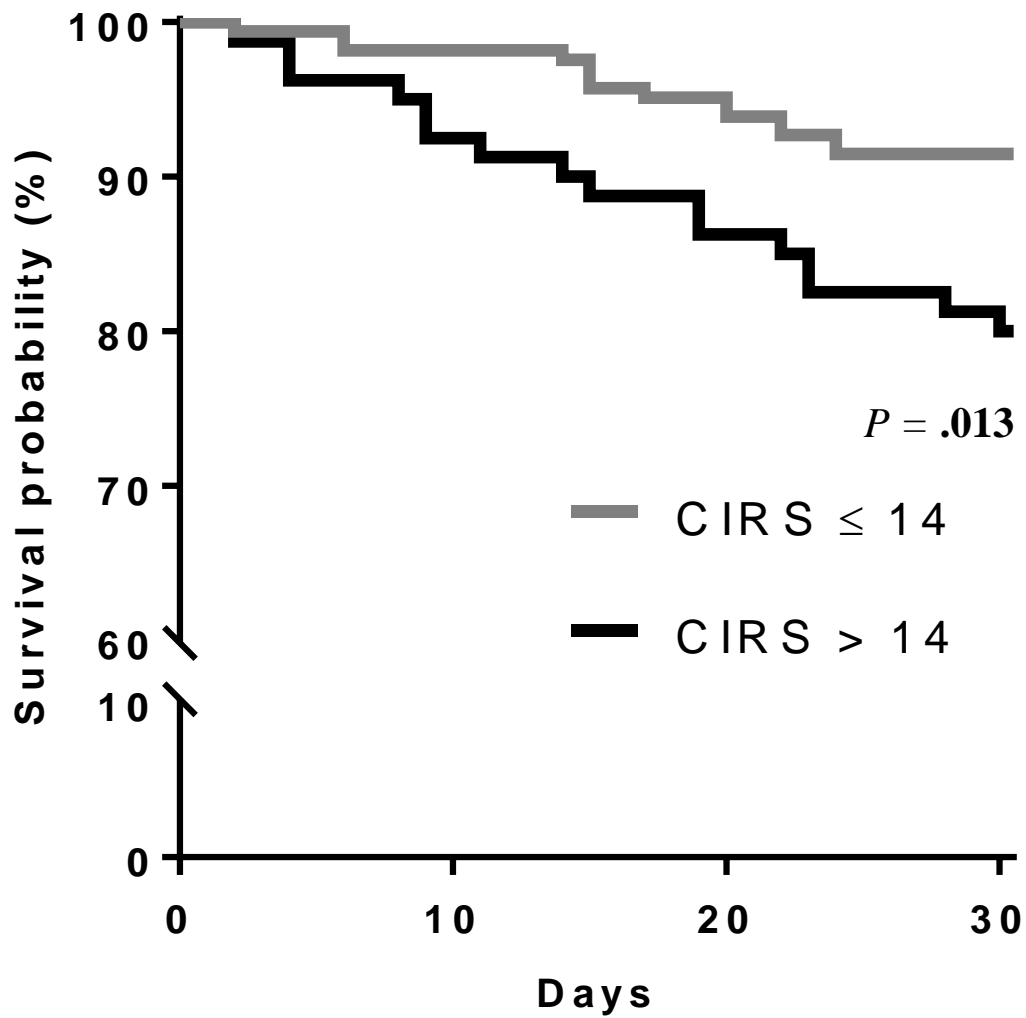
\*\*Organ failure was assessed when intravenous use of diuretics and/or rise in serum creatinine level  $\geq 1.5$  times the premorbid level and/or need for oxygen during the course of CDI.<sup>+</sup>Rise in serum creatinine level:  $\geq 1.5$  times the premorbid level.<sup>±</sup>Severe comorbidity was assessed when baseline CIRS score > 14.



**Fig.1.**

Kaplan-Meier Plot of 30-day survival probability after *Clostridioides difficile* infection diagnosis comparing patients with or without organ failure.

Organ failure was assessed when use of diuretics or rise in serum creatinine level  $\geq 1.5$  times the premorbid level or need for oxygen.



**Fig.2.** Kaplan-Meier Plot of 30-day survival probability after *Clostridioides difficile* infection diagnosis according to Cumulative Illness Rating Scale (CIRS) score (cut-off of 14).