



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

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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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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.

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Abstract

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

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

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

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

Results: Included patients numbered 247; mean age was 87.2 (SD 5.4). Most of the CDI incidences (66.4%) were health-care associated infections with 81% diagnosed within 30 days of hospitalization; CIRS mean score was 16.6 (SD 6.6). Markers of severity ≥ 3 included 97 patients (39.3%). Metronidazole was the main initial treatment (51.0%). *Clostridioides difficile* infection in the elderly was associated with a 30-day mortality of 12.6%. Multivariate analysis showed that baseline CIRS score (HR 1.06 per one-point increase, 95% CI 1.00-1.12) and evidence of cardiac, respiratory, or renal decompensation (HR 3.04, 95% CI 1.40-6.59) 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.^{1,2} Over the
31 past ten years, there has been an important increase in both incidence and severity of CD
32 infection (CDI).³ 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.⁴ The risk of recurrence is estimated between 10 and 30%⁵⁻⁷
35 and all-cause CDI-related mortality ranges from 4.5% to 33.2%.⁸⁻¹² European guideline
36 documents based on several studies report that elderly patients are at increased risk of
37 recurrence and mortality.¹³ Patients aged 65 and older represent 60% to 70% of CDI cases.¹⁴⁻
38 ¹⁶ This age group is vulnerable because of more frequent and prolonged hospitalizations,
39 senescence of immune mechanisms and altered intestinal microbiota.¹⁷⁻¹⁹ Still, few studies
40 focused on patients over 75 years of age^{10,20-22} and predictive markers for short-term mortality
41 in this population are scarcely described.^{8,23,24} 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.

Methods

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

Data collection

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

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

creatinine level \geq 50% of the premorbid level and blood albumin $<$ 30g/L and severe underlying disease.¹³ Comorbidities were evaluated at admission by the Cumulative Illness Rating Scale (CIRS).^{25,26} Total CIRS score was recorded at the onset of CDI. We decided to use the median score to define comorbidity as severe. Organ failure was arbitrarily assessed during the course of CDI, relying either on intravenous use of loop diuretics for cardiac insufficiency, and/or need for oxygen, and/or rise in serum creatinine level \geq 50% of the premorbid level, for renal decompensation, according to the European guidelines documents.¹³

Treatment and outcome (length of hospital stay, recurrence of CDI, mortality) were recorded. Recurrence was defined as new CDI confirmed after the onset of a previous episode, provided the symptoms from the previous episode resolved for at least 48 hours after completion of initial treatment.

Data analysis

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

Results

Baseline characteristics

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

Course of infection

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

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

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

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

Discussion

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

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

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

The adequacy of European markers of the risk of severity with mortality, including comorbidities, were already reported on in previous meta-analysis and retrospective studies.^{7,29} Our results also showed that patients with ≥ 3 markers of risk of severity had a higher risk of mortality ($P = .022$).

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

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

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

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

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

Conclusions and Implications

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

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

Conflicts of interest

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

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Figure Legends

Fig.1.

Kaplan-Meyer 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 ≥ 1.5 times the premorbid level, or need for oxygen.

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 1Characteristics 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 (≥ 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 [†]	53 (21.5)
- Blood albumin $< 30\text{g/L}$	130 (52.6)
Severe comorbidity [‡]	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.¹³

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

[†]Rise in serum creatinine level ≥ 1.5 times the premorbid level.

[‡]Severe comorbidity (CIRS score > 14).

Table 2Risk 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)	.0037	1.08 [1.03 – 1.14]	.033	1.06 [1.00 – 1.12]
Organ failures during the course of CDI**, n (%)	46 (21.3)	16 (51.6)	.0005	3.64 [1.80–7.36]	.0048	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)	.0028	3.07 [1.50 – 6.62]	-	
Age (> 65 yrs)	216 (100)	31 (100)	-		-	
Leukocyte count > 15,000/mm ³	61 (28.2)	11 (35.5)	.39	1.39 [0.64 – 2.84]	-	
Rise in serum creatinine level ⁺	42 (19.4)	11 (35.5)	.048	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 [±]	64 (29.6)	16 (51.6)	.013	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.¹³

*per unit change

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

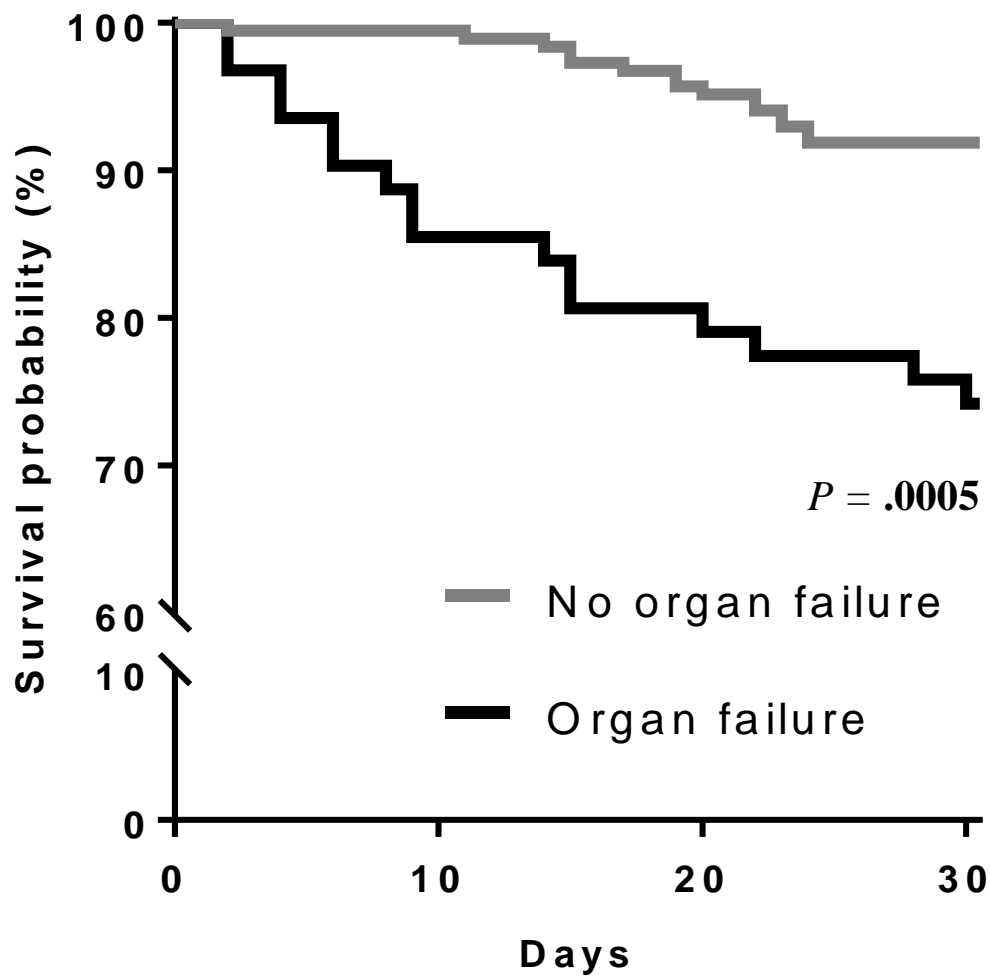


Fig.1.

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 ≥ 1.5 times the premorbid level or need for oxygen.

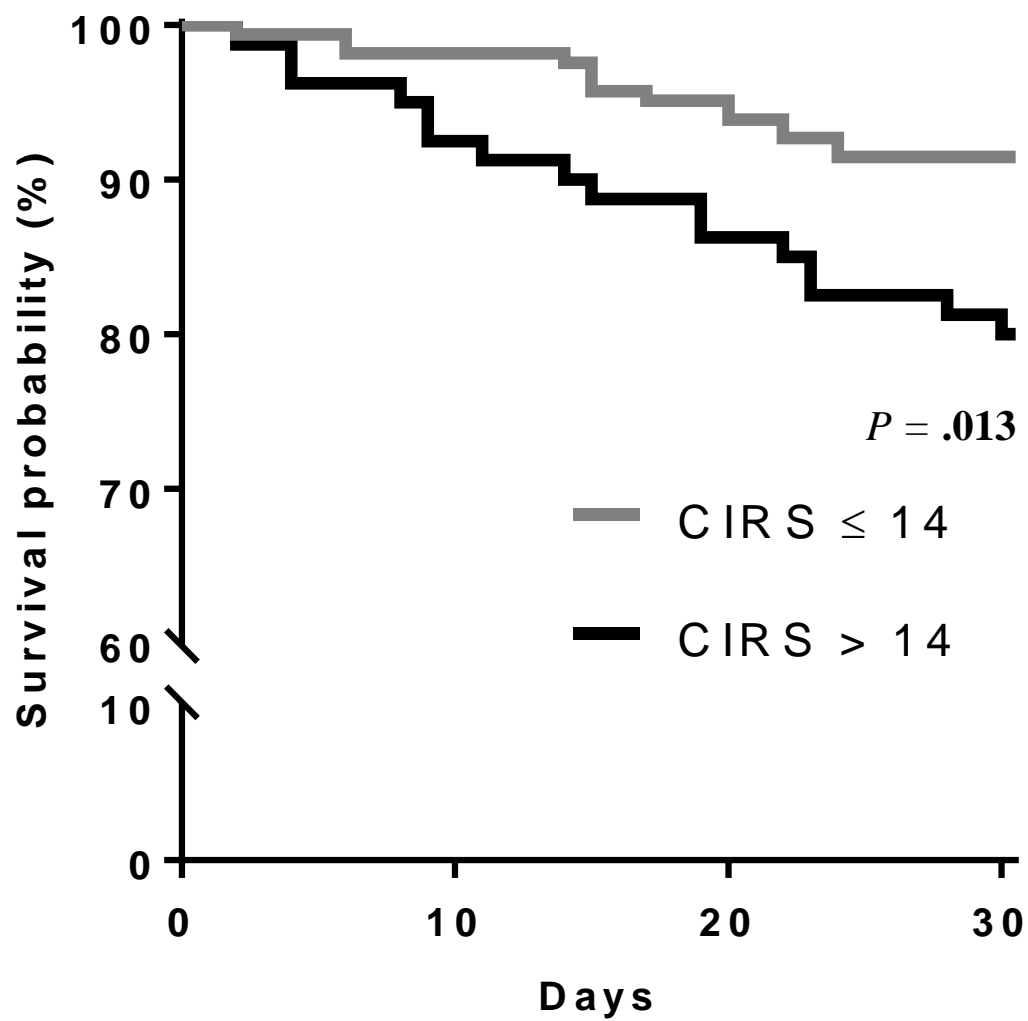


Fig.2. Kaplan-Meier Plot of 30-day survival probability after *Clostridioides difficile* infection diagnosis according to Cumulative Illness Rating Scale (CIRS) score (cut-off of 14).