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Poor Timing and Failure of Source Control Are Risk Factors for Mortality in Critically Ill Patients with Secondary Peritonitis --Manuscript Draft--

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Abstract:	Purpose To describe data on epidemiology, microbiology, clinical characteristics and outcome of adult ICU patients with secondary peritonitis, with special emphasis on antimicrobial therapy and source control. Methods Post hoc analysis of a multicenter observational study (Abdominal Sepsis Study, AbSeS) including 2621 adult ICU patients with intra-abdominal infection in 306 ICUs from 42 countries. Time-till-source control intervention was calculated as from time of diagnosis and classified into 'emergency' (<2 hours), 'urgent' (2-6 hours), and 'delayed' (>6 hours). Relationships were assessed by logistic regression analysis and reported as odds ratios (OR) and [95% confidence interval]. Results The cohort included 1077 cases of microbiologically confirmed secondary peritonitis. Mortality was 29.7%. The rate of appropriate empiric therapy showed no difference between survivors and non-survivors (66.4% vs . 61.3%, p=0.102). A stepwise increase in mortality was observed with increasing SOFA scores (19.6% for a value £4 to 55.4% for a value >12, p<0.001). The highest odds of death were associated with septic shock (OR 3.08 [1.42-7.00]), late-onset hospital-acquired peritonitis (OR 1.71 [1.16-2.52]) and failed source control evidenced by persistent inflammation at Day 7 (OR 5.71 [3.99-8.18]). Compared with 'emergency' source control intervention (<2 hours of diagnosis), 'urgent' source control was the only modifiable covariate associated with lower odds of mortality (OR 0.50 [0.34-0.73]). Conclusions 'Urgent' and successful source control were associated with improved odds of survival. Appropriateness of empirical antimicrobial treatment did not significantly affect survival suggesting that source control is more determinative for outcome.	
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Author Comments:	Dear Dr. Citerio, Editor-in-Chief, Dear Dr. Povoa, Associate-Editor, Thank you for the opportunity to re-revise the manuscript. We respectfully ask for your understanding for a particular aspect of the study... We followed the direction of the reviewer concerning defining a primary and secondary objective albeit that we do not feel completely comfortable with phrasing the study objectives in this way. As explained earlier, this is an epidemiological, exploratory study in which 'timing of source control' and 'empiric antimicrobial therapy' were variables, just like all others. Apparently, these covariates appeared to be of particular interest. Therefore, the reviewer asked us to define these variables as the covariates of primary interest. In our opinion, this is re-defining the study objective according to the study results. Evidently, it does not alter the study results, but it does not reflect our initial intentions. We look forward for an editorial decision. Yours sincerely, Stijn Blot On behalf of Gennaro De Pascale & Massimo Antonelli
Response to Reviewers:	We uploaded the responses to the reviewers as a supplementary file.

Poor Timing and Failure of Source Control Are Risk Factors for Mortality in Critically Ill Patients with Secondary Peritonitis

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Abstract

Purpose

To describe data on epidemiology, microbiology, clinical characteristics and outcome of adult ICU patients with secondary peritonitis, with special emphasis on antimicrobial therapy and source control.

Methods

Post hoc analysis of a multicenter observational study (Abdominal Sepsis Study, *AbSeS*) including 2621 adult ICU patients with intra-abdominal infection in 306 ICUs from 42 countries. Time-till-source control intervention was calculated as from time of diagnosis and classified into ‘emergency’ (<2 hours), ‘urgent’ (2-6 hours), and ‘delayed’ (>6 hours). Relationships were assessed by logistic regression analysis and reported as odds ratios (OR) and [95% confidence interval].

Results

The cohort included 1077 cases of microbiologically confirmed secondary peritonitis. Mortality was 29.7%. The rate of appropriate empiric therapy showed no difference between survivors and non-survivors (66.4% vs. 61.3%, $p=0.1$). A stepwise increase in mortality was observed with increasing SOFA scores (19.6% for a value ≤ 4 to 55.4% for a value >12 , $p<0.001$). The highest odds of death were associated with septic shock (OR 3.08 [1.42-7.00]), late-onset hospital-acquired peritonitis (OR 1.71 [1.16-2.52]) and failed source control evidenced by persistent inflammation at Day 7 (OR 5.71 [3.99-8.18]). Compared with ‘emergency’ source control intervention (<2 hours of diagnosis), ‘urgent’ source control was the only modifiable covariate associated with lower odds of mortality (OR 0.50 [0.34-0.73]).

Conclusions

‘Urgent’ and successful source control were associated with improved odds of survival. Appropriateness of empirical antimicrobial treatment did not significantly affect survival suggesting that source control is more determinative for outcome.

Keywords

Intra-abdominal infection; secondary peritonitis; source control; mortality; antimicrobial therapy

Trial registration number

ClinicalTrials.gov, NCT03270345. Registered on 13 May 2015

Introduction

Despite worldwide diffusion and implementation of international guidelines for the management of sepsis and septic shock, morbidity and mortality of severe intra-abdominal infections (IAI) remain high, along with many unavailable answers [1-3]. Peritonitis following anatomical disruption of gastro-intestinal tract is commonly called 'secondary', acquiring the definition of 'complicated' when the infections extends from the primary source to peritoneal cavity [4, 5]. Although secondary peritonitis represents the most frequent clinical picture in ICU admitted patients with complicated IAI, the right timing of source control, the role of empirical antimicrobial coverage and the clinical impact of antimicrobial resistant microorganisms are still a matter of debate [6, 7]. However, the recent multicenter AbSeS study, including 2621 patients with complicated IAI and sepsis, showed that, regardless the type of IAI, intensive care unit (ICU) mortality was strongly influenced by the nosocomial setting of acquisition, the presence of anatomical disruption and the occurrence of septic shock [8].

Source control certainly represents a key element in the management of secondary peritonitis, since, also before the antibiotic era, many patients with peritonitis were rescued only by surgical intervention [9, 10]. Depending on peritonitis-related characteristics, surgical source control may be particularly challenging and so far, there is no clear-cut way for evaluating the success of source control. While it seems evident that source control is achieved as soon as possible, executing a major surgical procedure in a clinically unstable patient may be a risk as well.

The importance of source control is not only an issue in bacterial peritonitis, but also in fungal infections. Two large multicenter cohort studies patients with uncontrolled intra-abdominal candidiasis showed a huge mortality rate, ranging between 60% and 90%, irrespective of administration of an adequate antifungal infection [11, 12].

Along with prompt control of the infection source, in critically ill patients with bacterial peritonitis, adequate empirical antibiotics are strongly recommended [13]. In two cohort studies involving more than 400 septic patients with complicated IAI, polymicrobial infections due to antimicrobial resistant bacteria mostly received inappropriate empirical therapy, leading to increased mortality [14, 15]. The optimal scheme and administration time is far from clearly established. In a post-hoc analysis of a randomized clinical trial, Montravers and colleagues reported empiric antimicrobial therapy with piperacillin-tazobactam to be associated with more overall post-operative clinical failure, despite the exclusion of cases with empiric antimicrobial therapy not covering all organisms cultured from blood and surgical samples [16].

In light of these considerations, [the primary objective of this study was to assess the relationship of timing of source control and appropriateness of empiric antimicrobial therapy with mortality](#)

in critically ill patients with secondary peritonitis. The secondary objective of this study is to describe the epidemiological, clinical, and microbiological profile of secondary peritonitis in the intensive care context.

Methods

Data recorded and definitions

We performed a secondary analysis of the data on secondary peritonitis from the ‘AbSeS’ multinational, observational study [8]. This cohort included critically ill adult patients with IAI from 309 ICUs and 42 countries between January and December 2016. Approval by established national, regional, or local Institutional Review Boards was expedited and granted. The study is registered at ClinicalTrials.gov (number NCT03270345). Protocols and procedures for the patients’ inclusion criteria, definitions, methods and collection of data have been previously reported [8]. Secondary peritonitis is defined according to the International Sepsis Forum Consensus Conference Definitions and only cases with gastro-intestinal tract perforation are considered. Cases were explored according to AbSeS-classification, i.e., setting of infection acquisition, anatomical barrier disruption, and severity of disease expression [17]. Secondary peritonitis could be either localized or diffuse peritonitis (i.e., contamination spread to entire abdominal cavity) [18]. Severity of disease expression is defined as either infection, sepsis, or septic shock [19]. Eligible cultures included intra-operative cultures, trans-abdominal fine-needle aspiration, blood cultures presumably related to the IAI, and cultures from abdominal drains sampled ≤ 24 hours post-surgery. Thresholds for resistance were those as reported by The European Committee on Antimicrobial Susceptibility Testing (EUCAST) [20]. Antimicrobial resistance was defined as methicillin-resistance for *Staphylococcus aureus*, vancomycin-resistance for enterococci, and for Gram-negative bacteria either production of extended-spectrum beta-lactamase (ESBL), carbapenem-resistance, or fluoroquinolone-resistance (resistance against ciprofloxacin, levofloxacin, or moxifloxacin). To assess relationships between resistance and mortality, we also used the definition of “difficult-to-treat” resistance for Gram-negative bacteria. This combines resistance to all tested carbapenem, beta-lactam, and fluoroquinolone agents, and is associated with worse clinical outcomes in bloodstream infection [21, 22]. Appropriate empiric antimicrobial therapy was defined as the administration of at least one drug with in vitro and clinical activity against the isolated pathogens and initiated within the first 24 hours of peritonitis diagnosis. Antimicrobial regimens that did not cover basic Gram-positive, Gram-negative, and anaerobic bacteria were as per definition considered inappropriate. Timing of source control intervention was defined as ‘emergency’ (i.e., < 2 hours

of peritonitis diagnosis), ‘urgent’ (between 2 and 6 hours), or ‘delayed’ (>6 hours) and based on simple explorative data (ESM-1). Success of source control was assessed 7 days post-diagnosis or earlier if the patient died within that time window. Source control failure represented either persistent inflammation (clinical evidence of a remaining source of infection) or the necessity of re-intervention following the initial approach (conservative management or source control intervention) [8]. Main outcome is ICU mortality with a minimum of 28 days of observation.

Data management and statistical analysis

Missing, extreme or implausible values were sent back to the study-ICU investigators for review. Where data remained questionable, the senior author (S.B.) made a final adjudication about study inclusion in agreement with the co-headinvestigator (D.V.). Essential data needed to keep cases in the AbSeS database included type of IAI, onset of infection, data on anatomical disruption, severity of disease expression, and microbiology or mortality. For the present secondary analysis, the availability of data on microbiology, empiric therapy, and mortality were all required. For all other variables missing values were not imputed. Simple descriptive statistics were used to characterize the study population, continuous data was summarized by median and interquartile range (IQR), categorical data as n (%). To assess relationships with mortality we used a logistic regression analysis with the logit link function. Variables considered for the logistic regression model included origin of infection acquisition, diffuse peritonitis, severity of disease expression, timing of source control intervention, source control achievement at day 7, antimicrobial resistance, *Candida* involvement, enterococcal involvement, appropriateness of empiric antimicrobial therapy, age, sex, underlying conditions, length of ICU stay, and geographic region. These variables were included irrespective of their relationship with mortality in univariate analysis. Feature selection and final fit is done through a stepwise forward and backward approach, depending on the Akaike Information Criterion (AIC) value (dropping and adding covariates that leads to the smallest AIC). As observational studies are susceptible for potential uncontrolled confounding, we calculated the E-value for our logistic regression model using the VanderWeele & Ding approach (ESM-2) [23]. Results of the logistic regression analyses are reported as odds ratio (OR) and 95% confidence intervals (CI). The Kaplan–Meier method was used for unadjusted survival analyses according to timing of source control intervention and source control outcomes at day 7.

Results

General characteristics

The AbSeS cohort contained 1794 patients with secondary peritonitis. Cases were excluded for missing data on microbiology (n=671), antimicrobial therapy (n=140), and mortality (n=24).

The final analysis included 1077 patients.

Characteristics of the study cohort are in Table 1. Most infections were late-onset hospital acquired. Half of the cases had diffuse peritonitis and nearly all patients presented with sepsis or septic shock. Malignancy, obesity, and diabetes were the most common comorbidities.

Data on source control are reported in Table 2. Most patients underwent infection source control within the first 6 hours with 55% within the first 2 hours of peritonitis diagnosis (i.e., the time of diagnosis/clinical suspicion prompting intervention).

Drainage, either surgically or percutaneously, was the initial source control approach in 95% of patients. At Day 7 in 60% of the cases source control was successful, requiring a second intervention in 109 patients, mainly due to anatomic leakage (Table 2).

Microbiology

Data on microbiology are reported in Table 3. A total of 1643 microorganisms have been isolated from 1077 patients. The majority were Gram-negative bacteria (48.5%), followed by Gram-positive bacteria (32.6%), anaerobic bacteria (9.2%) and yeasts (9.8%). Interestingly, inappropriate empiric antimicrobial therapy was associated with the isolation of *Klebsiella spp.* and non-fermentative rods (*Pseudomonas*, *Stenotrophomonas* and *Acinetobacter*) enterococci (either *E. faecium* and *E. faecalis*) and *Candida spp.* Finally, inappropriate empirical therapy was more frequently observed in case of antimicrobial resistance involvement.

Mortality

Mortality was 29.7% (Table 1). Non-survivors were older and were more likely to have comorbidities. Regarding IAI characteristics, non-survivors had more frequently a late-onset infection, diffuse peritonitis and septic shock. There were no differences between survivors and non-survivors in rate of multidrug resistance involvement, rate of appropriate empiric therapy, and SAPS II scores. However, mortality increased with increasing SOFA scores ($p<0.001$; ESM-3).

In terms of source control, basic patient characteristics regarding timing of source control is reported in ESM-4. Patients undergoing 'emergency' intervention (<2 hours from peritonitis diagnosis) showed a higher mortality compared with 'urgent' source control procedures (2-6

hours) (Table 2). Therefore, we compared pre-source control intervention characteristics of patients receiving ‘emergency’ source control (<2 hours of presentation, n=454) and patients with ‘urgent’ source control (between 2 and 6 hours, n=340). No difference between the groups was observed in terms of: serum lactate [2.5 mmol/L (IQR: 1.6-4.2) vs. 2.6 mmol/L (IQR: 1.6-4.2); p=0.972], pH [7.32 (IQR: 7.25-7.40) vs. 7.34 (IQR: 7.27-7.40); p=0.409], c-reactive protein [142 mg/L (IQR: 26-259) vs. 174 (IQR: 48-269); p=0.092], necessity for mechanical ventilation (73.3% vs. 75.0%; p=0.587), and SAPS 2 scores [50 (IQR: 38-62) vs. 48 (IQR: 39-58); p=0.252]. Shock (29.7% vs. 42.4%; p<0.001) and leucocytosis (29.7% vs. 40.3%; p=0.005) were more common among patients undergoing ‘urgent’ source control. Therefore, we executed sensitivity analyses on patients with ‘emergency’ and ‘urgent’ source control intervention, stratified for presence/absence of septic shock and leucocytosis; this did not alter the observation (ESM-5). Figure 2a illustrate unadjusted survival curves according to timing of source control intervention. Absolute mortality rates for ‘emergency’ and ‘delayed’ intervention were 35.9% and 28.6%, respectively, while mortality for patients receiving moderately postponed source control intervention was 23.6%. Successful source control at 7 days was more common among survivors (Table 2). Figure 2b illustrates unadjusted survival curves, according to source control achievement at day 7. Absolute mortality rates for the three groups were 18.7% for successful source control, 25.2% for source control requiring revision, and 55.7% for persistent inflammation: the latter performing the worst, even despite an assumed technically successful source control intervention.

Logistic regression analysis identified late-onset infections, diffuse peritonitis, persisting signs of inflammation, septic shock and underlying conditions (liver failure and malnutrition) as independent risk factors for death (Table 4). For this model, the associated E-value was 1.74 (lower limit 95% CI, 1.62) (ESM-2). Initiation of appropriate empirical antimicrobials was not associated with a significant reduced risk of ICU mortality (OR 0.78, 95% CI, 0.55-1.09). The impact of appropriateness of antimicrobial therapy on mortality was also not different according to source control outcomes (ESM-6). Conversely, the only modifiable condition associated with improved survival was a source control intervention performed between 2 and 6 hours from peritonitis diagnosis (OR 0.50, 95% CI 0.34-0.73).

Discussion

In this large cohort of critically ill patients with secondary peritonitis, we confirmed that the new AbSeS-classification, based on setting of acquisition, presence of anatomical disruption and severity of disease, strongly correlated with ICU mortality. ‘Emergency’ (<2 hours) and

‘delayed’ (>6 hours) source control was associated with worse clinical outcomes compared with an ‘urgent’ (2-6 hours) surgical approach, especially when a clinical picture of peritonitis with persistent inflammation was still present at day 7.

Secondary peritonitis represents the most frequent form of IAI affecting ICU patients. It is often complicated by generalized peritoneal inflammation and abscess formation due to extensive anatomical barriers disruption. If source control is not successfully achieved, inducing chronic serositis and colonization with difficult-to-treat microorganisms, it is called ‘tertiary’ [24, 25]. These definitions, mostly used in clinical trials, may be misleading, due to the overlapping of different clinical and prognostic features regarding anatomical barrier disruption, clinical severity and risk profile for multidrug-resistant pathogens [17, 26]. In the seminal *AbSeS* manuscript, a new classification focused on the setting of acquisition (community/healthcare/nosocomial), loss of anatomical integrity with either localized or diffuse peritonitis and severity of disease expression (infection, sepsis, septic shock), allowed to identify diseases-specific phenotypes which strongly correlated with ICU mortality [8]. Also, the data from this very large, selected, critically ill population with secondary peritonitis due to different intra-abdominal diseases (i.e., perforation, rather than diverticulitis or pancreatitis), highlight the detrimental importance to correctly classify a specific disease phenotype with the aim at stratifying the need of urgent and aggressive medical and surgical treatments. Patients with late-onset hospital-acquired infections, diffuse peritonitis due to loss of anatomical integrity and in septic shock (similarly with higher SOFA score values) presented the highest risk of mortality and needed prompt ICU admission, radiological diagnostic assessment and surgical consultation. Indeed, these results reinforce the usefulness of this new classification system for the design of more balanced and unbiased, future randomized trials in this field.

Almost all patients with secondary peritonitis were initially approached with source control, either surgically or percutaneously [8]. Although the crucial role of source control interventions in the management of IAIs is beyond any doubt, the correct approach (operative vs. conservative), timing (immediate vs. early vs. delayed after damage control) and type of procedures (surgical vs. percutaneous/endoscopic) are still a matter of debate [27]. On top of that, the source of infection in patients with septic shock may strongly influence final outcome, with lowest mortality rates observed in cholecystitis progressively increasing with perforated viscus and ischemic bowel (38.3% vs. 55.6% vs. 77.9%, respectively) [28]. *Azuhata et al.*, in a well conducted observational study on 154 patients with gastrointestinal perforation and

septic shock, demonstrated that time to surgery in hours significantly impacted 60-days outcome, with a survival rate of 0% when source control was delayed over 6 hours, under the condition that patients were supported with early haemodynamic stabilization [29]. In addition, in a very large prospective study, mainly represented by IAIs, those patients undergoing source control, although delayed over 12 hours from sepsis onset, showed reduced hospital mortality [30]. Analogue to our observation, Bloos et al. reported a significantly higher mortality rate when source control was executed >6 hours (42.9% vs. 26.7%; $p<0.001$) [31]. Likewise, our data support the adoption of an ‘urgent’ source control (2-6 hours), prioritizing haemodynamic stabilization, in very sick patients undergoing complex surgical procedures. Indeed, patients who received ‘emergency’ source control, despite a similar degree of clinical severity including the need of mechanical ventilation and vasopressors, showed a higher mortality compared with those ones where the surgical procedure was slightly postponed.

The clinical scenario of source control interventions in patients with IAIs may be very different according to type of infections and patients’ clinical status. Among 785 procedures performed in 353 patients, half of the patients required multiple interventions and effective control of the source of infection was ultimately obtained only in 67% of the cases [32]. Also in our cohort, about 60% of the patients obtained at first attempt a successful source control, with 139 subjects needing additional surgical interventions within the first 7 days. Interestingly, the latter group presented an initial survival advantage, probably due to a bias in patients who did not undergo several surgical interventions for the severity of their conditions. Conversely, it is not surprising that patients who presented a clinical picture of un-resolving inflammation showed the highest mortality rate, along with persistent organ failures and uncontrolled source of infection.

Finally, in our large cohort of critically ill patients with secondary peritonitis, infections due to antimicrobial resistant microorganisms (either bacteria or fungi) were at increased risk of inappropriate antimicrobial treatment, which, however, did not influence final clinical outcome. This observation, apparently in contrast with current knowledge on the crucial role of prompt adequate antimicrobials in severe infections [33-36], does only reinforce the need to prioritize the role of clinical stabilization and adequate source control over an intervention focused only on optimal antimicrobial therapy. Nevertheless, in presence of germs resistant to multiple antimicrobials, rescue drugs, although active ‘in vitro’, may be suboptimal ‘in vivo’ due to pharmacokinetic and pharmacodynamics (PK/PD) limitations (i.e. colistin, aminoglycosides) [37, 38].

We acknowledge several limitations of this study. First, although prospective, the observational design is prone to multiple confounding factors not allowing to generalize our results. At the same line, we cannot rule out unmeasured confounding. However, E-value calculation indicated that any missing covariate should have a **robust** relationship to annihilate the relationship between emergency source control and mortality (ESM-2). Second, there was not a predefined common approach to source control and its definition was discretionary, according to different site sub-investigators. Third, we do not have in-depth information on timing and type of haemodynamic support, especially during source control procedures, thus missing potentially relevant elements. Fourth, antimicrobial appropriateness is established on ‘in vitro’ susceptibility criteria, but PK/PD features and exclusively considers the first 24h timeframe; aspects such as appropriate therapy initiated after the first 24 hours, synergistic combinations, and de-escalation practices could not be considered. Finally, by including different types of infection and surgical interventions, we were not able to verify whether the observed results may be valid in specific subgroup populations.

Conclusions

In critically ill patients with secondary peritonitis, hospital-acquired infections, diffuse peritoneal inflammation and septic shock were strong predictors of poor clinical outcome. Failure of source control as characterized by persistent signs of inflammation rather than the need for additional source control intervention, was strongly associated with mortality. Concerning the timing of source control ‘emergency’ intervention (i.e., within 2 hours) was associated with worse outcomes compared with cases receiving source control within the first 6 hours despite an apparently similar degree of disease severity. We cautiously assume that initial hemodynamic stabilization before source control intervention may be preferred. On the other hand, we support the idea of aiming for source control as soon as hemodynamic stability has been achieved. Well-designed clinical trials involving most severe patients with similar risk profile of ICU mortality, should assess the effect of early vs. later source control interventions, and the potential relationship with the timing of haemodynamic stabilization and appropriate antimicrobials prescription.

Take home message

This multinational study including data from microbiologically documented secondary peritonitis showed that moderately postponed (2 to 6 hours) and successfully source control significantly predicted ICU survival. Appropriate empirical antimicrobial treatment did not reduced mortality which was strongly increased by acquiring infection in the hospital setting, presence of diffuse peritoneal inflammation, and septic shock.

Tweet

Role of source control in secondary peritonitis: timely and successfully interventions reduced mortality in 1077 critically ill patients.

Declaration

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Conflicts of interest/competing interests

- Received grants related to the submitted work: S. Blot (Pfizer)
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 - M. Antonelli (Fresenius, Pfizer, Toray);
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 - E. Maseda (Astellas Pharma, Pfizer, MSD);
- All other authors: no conflict of interest.

Author's contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by De Pascale, Blot and Antonelli and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

Approval by established national, regional, or local institutional review boards was expedited and granted.

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Table 1 – Characteristics of critically ill patients with secondary peritonitis according to survival status

Variable	All patients (n=1077)	Survivors (n=757)	Non-survivors (n=320)	p-value
Age, years	67 (55-75)	64 (52-73)	73 (64-80)	<0.001
Sex, male	599 (55.6)	416 (55.0)	183 (57.4)	0.480
SAPS II score at ICU admission	49 (39-60)	49 (39-60)	48 (36-60)	0.405
Generic characteristics of the intra-abdominal infection				
Setting of infection acquisition				<0.001
Community-acquired	371 (34.4)	278 (36.7)	93 (29.1)	
Healthcare-associated or early-onset hospital-acquired	259 (24.0)	196 (25.9)	63 (19.7)	
Late-onset hospital-acquired	447 (41.5)	283 (37.4)	164 (51.2)	
Anatomical barrier disruption				
No disruption	0	0	0	0.004
Disruption with localized peritonitis	529 (49.1)	397 (52.3)	133 (41.6)	
Disruption with diffuse peritonitis	547 (50.8)	360 (47.6)	187 (58.4)	
Severity of disease expression				
Infection without sepsis	74 (6.9)	62 (8.2)	12 (3.8)	<0.001
Sepsis	687 (63.8)	507 (67.0)	180 (56.3)	
Septic shock	316 (29.3)	188 (24.8)	128 (40.0)	
Upper or lower GI-tract perforation*				0.095
Upper	233 (21.6)	154 (20.3)	79 (24.7)	
Lower	693 (64.3)	498 (65.8)	195 (60.9)	
Underlying conditions				
Chronic pulmonary disease	137 (12.9)	84 (11.1)	53 (16.6)	0.014
Malignancy	326 (30.3)	208 (27.5)	118 (36.9)	0.002
Neurologic disease	64 (5.9)	32 (4.2)	32 (10.0)	<0.001
Liver disease	40 (3.7)	20 (2.6)	20 (6.3)	0.004
Congestive heart failure	25 (2.3)	29 (3.8)	34 (10.6)	<0.001
Peripheral vascular disease	60 (6.6)	37 (4.9)	23 (7.2)	0.133
Diabetes mellitus	166 (15.4)	98 (12.9)	68 (21.3)	0.001

	Immunosuppressed status	120 (11.1)	87 (11.5)	33 (10.3)	0.574
	Malnutrition (body mass index <20)	72 (6.7)	41 (5.4)	31 (9.7)	0.010
	Obesity (body mass index ≥30)	299 (27.7)	226 (29.9)	73 (22.8)	0.018
	Multidrug antimicrobial resistance (with high-level resistance for Gram-negative bacteria)**	109 (10.1)	75 (9.9)	34 (10.6)	0.721
	Appropriate empiric antimicrobial therapy	699 (64.9)	503 (66.4)	196 (61.3)	0.102
	Additional infections complicating the course				
	Pneumonia	164 (15.2)	124 (16.4)	40 (12.5)	0.105
	Community-acquired	24 (2.2)	13 (1.7)	11 (3.4)	
	Healthcare-associated	61 (5.7)	47 (6.2)	14 (4.4)	
	Ventilator-associated	79 (7.3)	64 (8.5)	15 (4.7)	
	Bloodstream infection	81 (7.5)	55 (7.3)	26 (8.1)	0.625
	Pyelonephritis	51 (4.7)	39 (5.2)	12 (3.8)	0.322
	Central nervous infection	3 (0.3)	2 (0.3)	1 (0.3)	NA
	Surgical site infection	81 (7.5)	56 (7.4)	25 (7.8)	0.813
	Osteomyelitis	1 (0.1)	0	1 (0.3)	NA
	Other	96 (8.9)	68 (9.0)	28 (8.8)	0.902

Applying Bonferroni correction, the threshold for statistical significance was $p < 0.00208$, implying a family-wise error rate of 0.049.

*Not reported, n=151

**Defined as either methicillin-resistance for *Staphylococcus aureus*, vancomycin-resistance for enterococci, Difficult-To-Treat Gram-negative bacteria (i.e., resistance to all carbapenems, all beta-lactams, and all fluoroquinolones), and fluconazole resistance for *Candida* spp.

Table 2 – Source control interventions and achievements

Variable		Survivors (n=757)	Non-survivors (n=320)	p
Time till source control intervention*				<0.001
	‘Emergency’ (<2 hours)	291 (42.3)	163 (56.0)	
	‘Urgent’ (2 to 6 hours)	265 (38.5)	75 (25.8)	
	‘Delayed’ (>6 hours)	132 (19.2)	53 (18.2)	
Initial source control approach (combinations possible)**				
Drainage		664 (95.8)	282 (94.9)	0.545
	Surgical drainage	636	271	
	Peritoneal lavage	207	78	
	Percutaneous drains	142	60	
	Debridement of necrosis	131	50	
Decompressive surgery		49 (7.3)	16 (5.7)	0.395
Restoration of anatomy & function		199 (29.5)	94 (33.7)	0.200
Source control achievement at day 7				<0.001
	Successful	522 (69.0)	120 (37.5)	
	Failure, persistent inflammation	131 (17.3)	165 (51.6)	
	Failure, additional intervention required ≤7 days	104 (13.7)	35 (10.9)	
Reasons for additional intervention				
	Anastomotic leakage	56 (7.4)	18 (5.6)	0.293
	Obstruction	8 (1.1)	1 (0.3)	NA
	Abdominal compartment syndrome	5 (0.7)	4 (1.3)	NA
	Bleeding	4 (0.5)	2 (0.6)	NA
	Ischaemia	9 (1.2)	3 (0.9)	NA
	Abscess formation	6 (0.8)	2 (0.6)	NA

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	Explorative laparotomy for persistent inflammation	8 (1.1)	3 (0.9)	NA
	Other	9 (1.2)	3 (0.9)	NA

Not reported: *n=98; **n=87; NA, not applicable

Table 3 - Micro-organisms isolated from cultures sampled in critically ill patients with secondary peritonitis

Micro-organism	Inappropriate empiric antimicrobial therapy (n=378)	Appropriate empiric antimicrobial therapy (n=699)	p
Gram-negative bacteria	279 (73.8)	517 (74.0)	0.956
Enterobacterales	230 (60.8)	469 (67.1)	0.040
Citrobacter sp.	2 (0.5)	8 (1.1)	0.508
Citrobacter freundii	4 (1.1)	11 (1.6)	0.594
Escherichia coli	146 (38.6)	49.9 (49.9)	<0.001
Enterobacter aerogenes	7 (1.9)	18 (2.6)	0.452
Enterobacter cloacae	14 (3.7)	33 (4.7)	0.435
Hafnia alvei	2 (0.5)	3 (0.4)	0.999
Morganella morganii	6 (1.6)	10 (1.4)	0.839
Klebsiella sp.	26 (6.9)	14 (2.0)	<0.001
Klebsiella oxytoca	12 (3.2)	20 (2.9)	0.773
Klebsiella pneumoniae	60 (15.9)	71 (10.2)	0.006
Proteus sp.	2 (0.5)	12 (1.7)	0.101
Proteus mirabilis	17 (4.5)	27 (3.9)	0.616
Providencia sp.	0	2 (0.3)	NA
Salmonella enterica	2 (0.5)	2 (0.3)	0.616
Serratia marcescens	4 (1.1)	1 (0.1)	0.054
Enterobacterales, other	6 (1.6)	7 (1.0)	0.401
Non-fermenting bacteria	94 (24.9)	73 (10.4)	<0.001
Pseudomonas aeruginosa	50 (13.2)	46 (6.6)	<0.001
Pseudomonas sp. (other or NI)	9 (2.4)	2 (0.3)	0.002
Stenotrophomonas maltophilia	6 (1.6)	1 (0.1)	0.009
Acinetobacter baumannii	28 (7.4)	13 (1.9)	<0.001
Acinetobacter sp. (other or NI)	14 (3.7)	14 (2.0)	0.109
Other Gram-negative bacteria			
Haemophilus influenzae	2 (0.5)	1 (0.1)	0.283
Gram-positive bacteria	216 (57.1)	319 (45.6)	<0.001
Staphylococci	45 (11.9)	90 (12.9)	0.700
Staphylococcus aureus	13 (3.4)	27 (3.9)	0.866
Coagulase-negative staphylococci	25 (6.6)	49 (7.0)	0.900
Staphylococcus sp. (other or NI)	10 (2.6)	15 (2.1)	0.603
Enterococci	167 (44.2)	184 (26.3)	<0.001
Enterococcus faecalis	76 (20.1)	93 (13.3)	0.003
Enterococcus faecium	75 (19.8)	75 (10.7)	<0.001
Enterococcus sp. (other or NI)	32 (8.5)	26 (3.7)	0.001

	Other Gram-positive bacteria			
	<i>Streptococcus</i> Group A, B, C, G	18 (4.8)	60 (8.6)	0.021
	<i>Streptococcus pneumonia</i>	4 (1.1)	1 (0.1)	0.054
	<i>Streptococcus viridans</i>	6 (1.6)	19 (2.7)	0.239
	<i>Corynebacterium</i>	1 (0.3)	4 (0.6)	0.478
	Anaerobe bacteria*	45 (11.9)	106 (15.2)	0.141
	Candida sp.	118 (31.2)	43 (6.2)	<0.001
	Specific resistance patterns			
	ESBL-producing Gram-negative bacteria	148 (39.2)	86 (12.3)	<0.001
	Fluoroquinolone-resistant Gram-negative bacteria	133 (35.2)	108 (15.5)	<0.001
	Carbapenem-resistant Gram-negative bacteria	81 (21.4)	19 (2.7)	<0.001
	Difficult-to-Treat Gram-negative bacteria**	49 (13.0)	12 (1.7)	<0.001
	Methicillin-resistant <i>Staphylococcus aureus</i>	6 (1.6)	9 (1.3)	0.689
	Vancomycin-resistant enterococci	35 (9.3)	5 (0.7)	<0.001
	Fluconazole-resistant/dose-dependent <i>Candida</i> sp.	10 (2.6)	2 (0.3)	<0.001

Table reports n patients positive (% of total number of patients with cultures sampled)

ESBL, extended-spectrum beta-lactamase

*No differences in species level detected (data not shown)

**Combines resistance to all beta-lactam antibiotics, all carbapenems, and all fluoroquinolones.

Table 4 – Adjusted relationships with mortality in critically ill patients with secondary peritonitis

Variable		Odds ratio (95% confidence interval)
Age (per year increase)		1.05 (1.04 – 1.06)
Setting of infection acquisition		
	Community-acquired infection	Reference
	Early-onset hospital-acquired infection (≤ 7 days)	0.74 (0.46-1.19)
	Late-onset hospital-acquired infection (> 7 days)	1.71 (1.16-2.52)
Anatomical disruption		
	Anatomical disruption with localized peritonitis	Reference
	Anatomical disruption with diffuse peritonitis	1.34 (0.96-1.87)
Severity of disease expression		
	Infection	Reference
	Sepsis	1.61 (0.76-3.42)
	Septic shock	3.08 (1.42-7.00)
Underlying conditions		
	Chronic pulmonary disease	1.40 (0.88-2.23)
	Neurologic disease	1.56 (0.83-2.92)
	Liver failure	3.77 (1.70-8.38)
	Congestive heart failure	1.72 (0.92-3.23)
	Diabetes mellitus	1.49 (0.97-2.30)
	Malnutrition (body mass index < 20)	2.45 (1.28-4.71)
	Obesity (body mass index ≥ 30)	0.70 (0.48-1.02)
Appropriate empiric antimicrobial therapy		0.78 (0.55-1.09)
Time-to-source control intervention		
	‘Emergency’ (< 2 hours)	Reference
	‘Urgent’ (2 to 6 hours)	0.50 (0.34-0.73)
	‘Delayed’ (> 6 hours)	0.90 (0.58-1.41)
Source control achievement at day 7		
	Success	Reference
	Failure, persistent signs of inflammation	5.71 (3.99-8.18)
	Failure, additional intervention required following initial approach	1.54 (0.94-2.54)

Legend. An identical regression model was executed after recoding the variable “time-to-source control intervention” with ‘urgent’ source control being the reference category. This resulted in ‘emergency’ source control having a relationship with mortality of OR 1.99 (95% CI 1.37 – 2.91). This allowed the calculation of the E-value on the relationship of ‘emergency’ source control with mortality (ESM-2).

Fig 1 – Study flow chart

Legend.

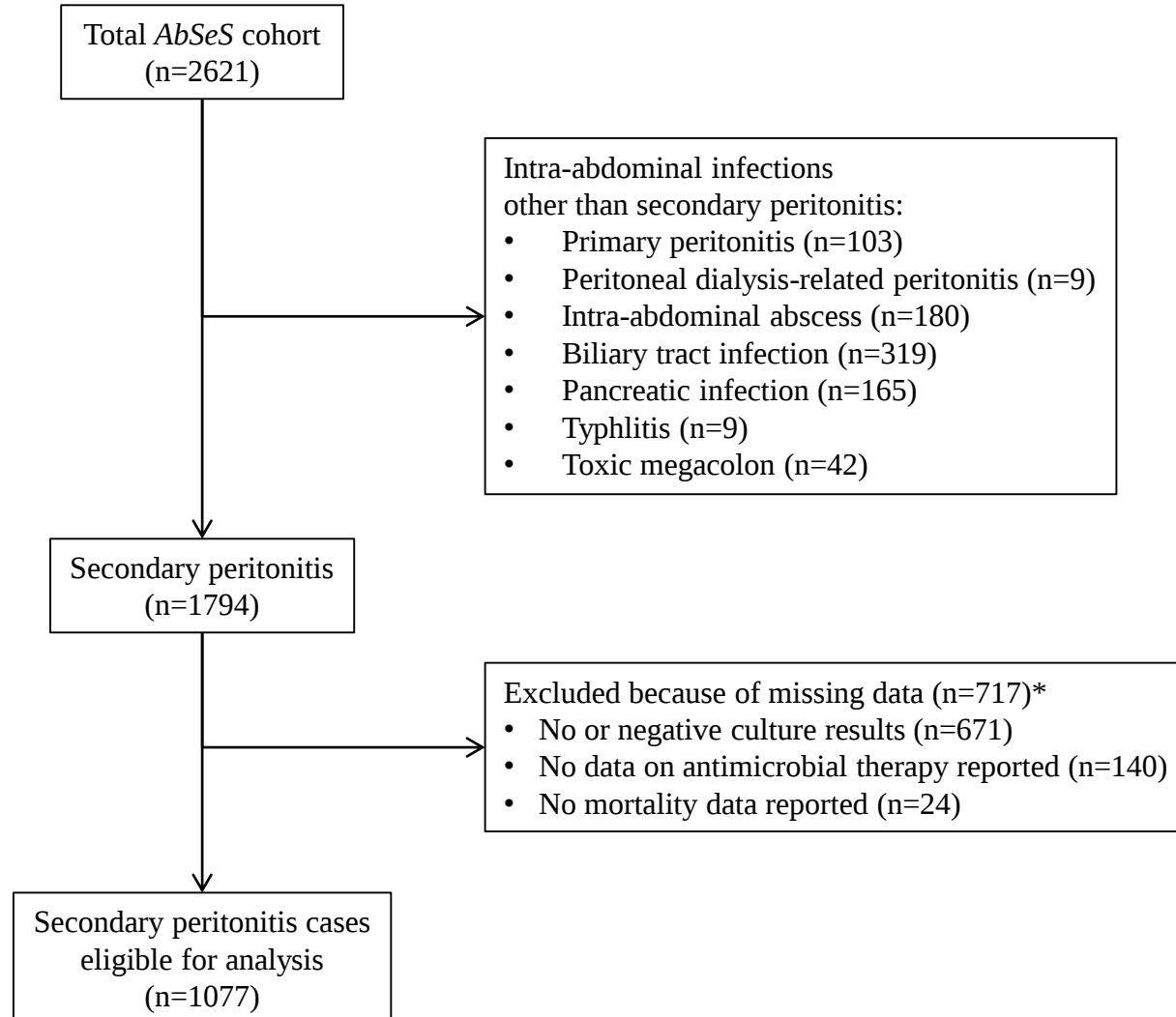
*In 118 patients more than one variable was missing

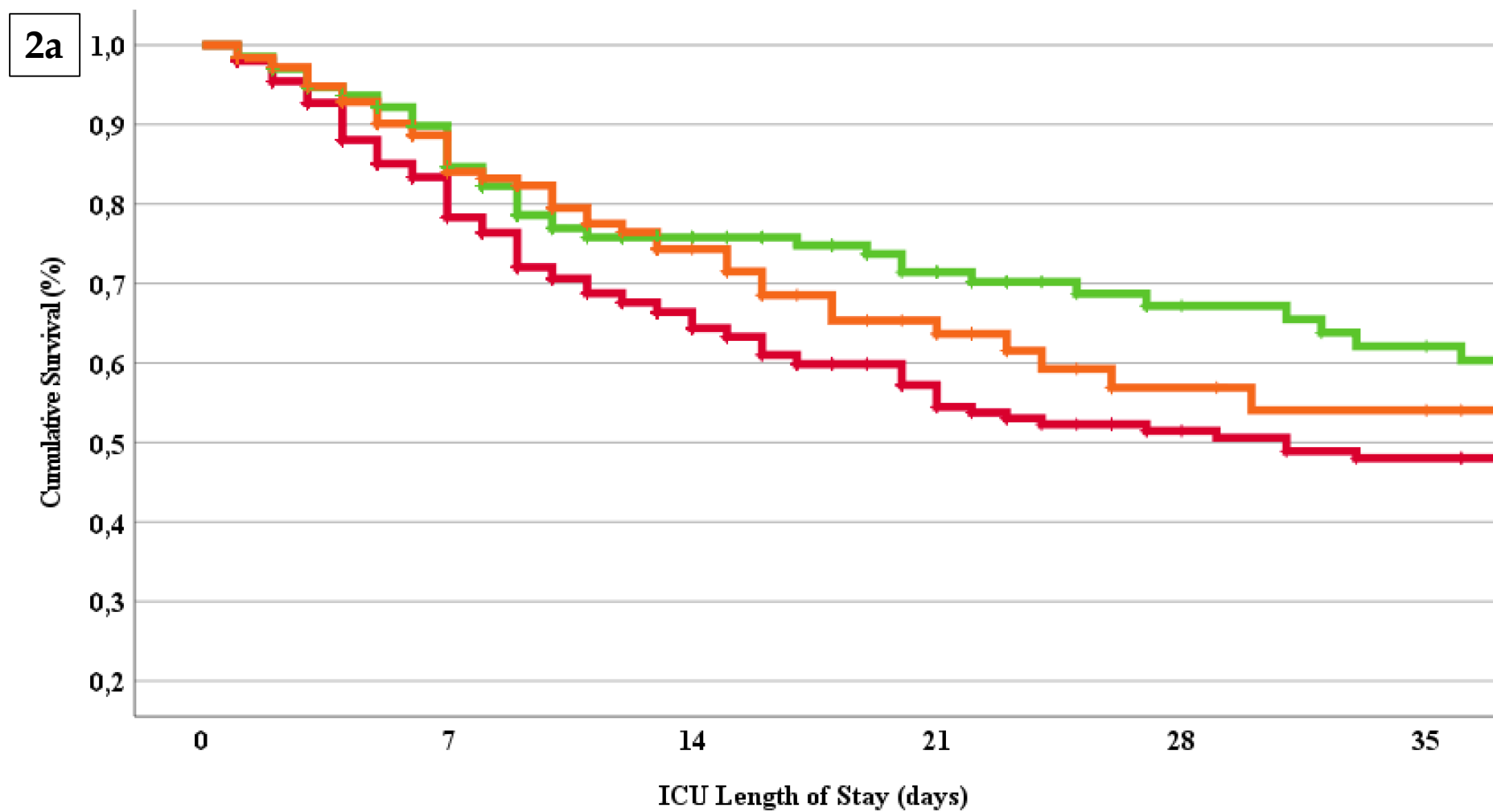
Fig 2 – Survival curves according to timing of source control intervention (2a) and source control outcomes at day 7 (2b)

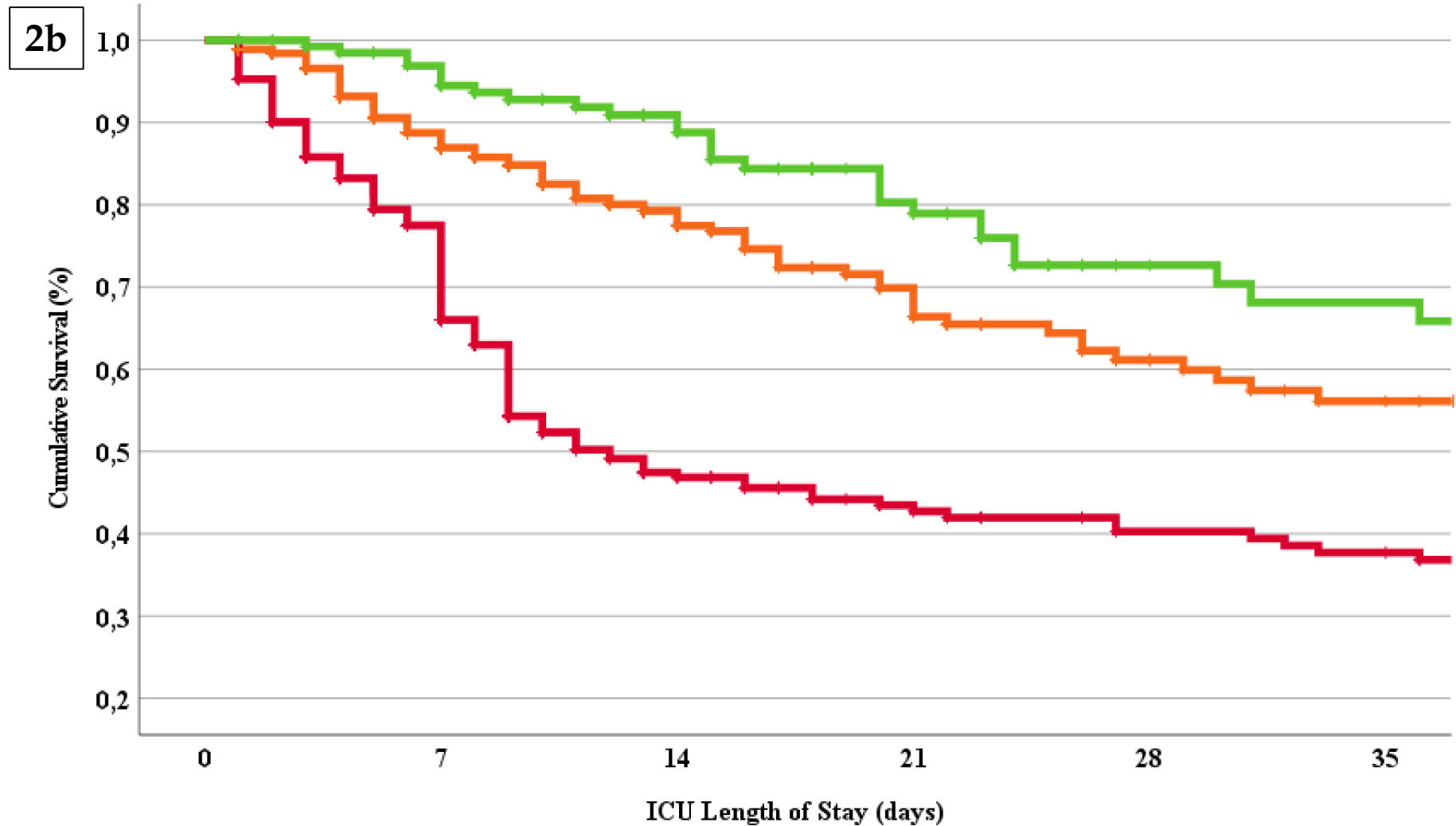
Legend.

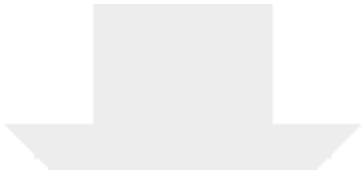
2a. Green curve represents cases with ‘urgent’ source control intervention (between 2 and 6 hours); orange curve represents cases with ‘delayed’ source control intervention (>6 hours); red curve represents cases with ‘emergency’ source control intervention (<2 hours); log rank test: $p=0.005$

2b. Green curve represents cases with successful source control; orange curve represents cases requiring additional source control intervention; red curve represents cases with persistent inflammation; log rank test: $p<0.001$

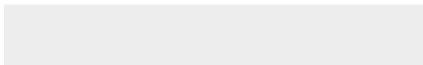
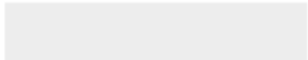


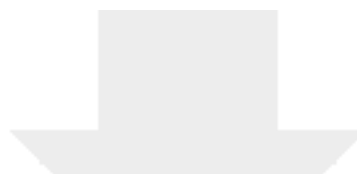






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