ORIGINAL ARTICLE

A retrospective study of factors affecting mortality in patients with complicated intra-abdominal infection

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ABSTRACT

Introduction: Complicated intraabdominal infection (cIAI) is a widespread infection of intraabdominal organs and it has a high mortality rate. Patients might present with various factors affecting the prognosis of this condition. This study aims to analyze the various factors of cIAI patients and to find their association with mortality during the treatment in hospitals.

Materials and Methods: A cross-sectional retrospective single-center study was conducted between 2020 and 2021 using 265 patients' medical records at Dr. Soetomo General Hospital in Surabaya, Indonesia. Various data regarding patient factors at the time of admission were recorded and analyzed to find the association with mortality during treatment. Chi-square and logistic regression test were used to verify our hypothesis statistically.

Results: The patient factors in this study were predominantly male patients (65.3%), younger age (86.4%), cIAI caused by appendicitis (35.5%), and normal nutritional status (73.2%). The overall mortality rate during treatment in this study was 34.7%. Five factors were significantly associated with mortality in cIAI patients during treatment ($p<0.05$), which are: older than 65 years old (OR: 2.85; 95% CI 1.11–7.31), having comorbid disease (OR: 7.92; 95% CI 2.05–30.63), septic shock on admission (OR: 5.56; 95% CI 2.40–12.91), treatment duration more than 3 days (OR: 2.52; 95% CI 1.24–5.15), and SOFA score more than 2 points (OR: 12.14; 95% CI 2.70–54.72).

Conclusion: Patient factors including age, comorbid disease, septic shock on admission, treatment duration, and SOFA score were significantly associated with the incidence of mortality during the treatment in cIAI patients.

KEYWORDS:
Complicated Intraabdominal Infection, peritonitis, mortality

INTRODUCTION

Complicated intra-abdominal infection (cIAI) is a widespread infection of intra-abdominal organs that results in localized peritonitis, intra-abdominal abscess, and diffuse peritonitis. This condition has a substantial impact since it significantly increases morbidity and mortality.[1] The CIAOW global study states that 16% of cIAI patients fall into critical condition and 10% of cases die while receiving therapy.[2] The global AbSeS study noted that the cIAI global mortality rate was 29.1% and estimated to reach 40.3–54.9% if they fell into septic shock.[3] Sartelli et al.[4] revealed that when there is coexistence with sepsis, the mortality rate of cIAI increases from 1.2% to 4.4%, even reaching 67.8% in septic shock.[4] Epidemiologic data of cIAI in Indonesia at six reputable medical institutes identified 608 cases of cIAI over a 2-year period with a mortality rate of 16.6%.[5,6]

Intra-abdominal sepsis is a challenge in the surgery field, especially its management in developing countries. The survival rate of cIAI patients is influenced by various factors such as bacterial pathogenicity, prompt and adequate source control, appropriate antibiotic administration, and intrinsic risk factors of the patient.[7] Patient sepsis-related risk factors are strong predictors in assessing the mortality of cIAI patient.[8,9] Early detection of septic conditions and taking prompt action to prevent cIAI patients' progression into septic conditions will increase their survivability. Although there have been multiple publications of cIAI worldwide, current studies that describe the characteristics of cIAI patient factors and their association with mortality during treatment are still limited. This study aims to analyze the characteristics of various factors in cIAI patient and their association with mortality during treatment at one of health centers in Indonesia.

MATERIALS AND METHODS

Study design

A retrospective cohort study was conducted using data from medical records of patients who received treatment at our healthcare center, Dr. Soetomo General Hospital Surabaya, Indonesia, between 2020 and 2021. We searched for the association between patients' factors at the time of admission to our emergency department with the mortality during the treatment. This study was approved by the ethics committee in our hospital and all researchers have undergone a certified Good Clinical Practice course. All data used in this study were anonymous and information regarding patients' personal data was kept confidential.

Patient data and factors

We collected patient medical records in 2020–2021 by consecutive total sampling according to the following inclusion criteria: an Indonesian, men/women aged over 18 years, diagnosed with cIAI, or suffering from secondary/tertiary peritonitis, intra-abdominal abscess, and

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underwent source control surgery during hospitalization. Incomplete medical record data for analysis will be excluded from this study. Cases of primary peritonitis and pancreatitis were not analyzed.

The study recorded several factors of the patient present to the emergency department, including gender, age, referral/non-referral, etiology of cIAI, nutritional status, comorbid disease, septic shock event, immune status, time-to-treatment, duration of source control surgery, and Sequential Organ Failure Assessment (SOFA) score based on Sepsis-3 global criteria. We performed a binary classification of several factors to facilitate statistical analysis of the association to patient mortality at the end of treatment. The patient's age was classified into two classes, with those who are > 65 years classified as geriatric. The home address is recorded according to the patient's domicile to know whether the patient was referred or not (primary patient in our hospital). The nutritional status is divided based on the classification of body mass index into excess nutrition, normal, and undernourished groups.

Factors such as comorbid disease, septic shock status, and immune status at the time of admission to the emergency department were also recorded. A comorbid disease is defined as any disease which is not directly related to cIAI itself, that co-exists in the patient diagnosed with cIAI. Those diseases can be cardiovascular (hypertension, heart failure), lung (chronic obstructive pulmonary disease, acute respiratory distress syndrome), renal (chronic renal failure, acute kidney injury), liver (elevated liver function, hepatitis, cirrhosis hepatitis), and malignancy. This information was retrieved from the patient's medical record. The immune status was analyzed with the history taking. Immunosuppression is a condition when patients have a suppressed immune system such as chronic use of immunosuppressants, undergoing chemotherapy, or suffer from systemic disease involving a lymphatic (lymphoma) or immune system. Shock septic is evaluated based on patient condition at the time of arrival to our emergency department. We classified patient into the septic shock group if the Mean Arterial Pressure (MAP) was below 65 mmHg (with no vasopressor). Time-to-Treatment (days) is defined as time consumed from the onset of symptoms appear to the time when patient received treatment at our hospital. The duration of surgery is the time (minutes) required by the patient during source control surgery. SOFA scores are divided into two classes, with score of >2 considered as high-risk. Each patient was then monitored until the completion of their course of treatment and it was noted whether they had survived or not. This condition is listed as the patient's outcome.

Statistic analysis

Each data of patient factors will be presented in frequency. The mean, median, and standard deviation were calculated for each data with a ratio scale (age, duration of surgery, time-to-treatment, and SOFA score). Factor data of nominal and ordinal scale is analyzed for statistical association, while the outcome is analyzed with chi-square test. We aim to explore factors that are significantly associated with the incidence of mortality during treatment. The second stage of statistical test is to perform a Logistics Regression test on factors that are already proven to be associated in previous analysis. The significance value of this study was $p<0.05$. The study also calculated the value of Odds Ratio (OR) and 95% Confidence Interval (95% CI) on factors that were significantly related to patient mortality. All statistical tests was done using Statistical Package for Social Science computer application IBM SPSS Statistics for Windows version 25; IBM Corp., Armonk, NY, USA.

RESULTS

Characteristics of patient factors

During the period of data collection, 278 cIAI patients were obtained from a total of 2.330 surgical patients who presented to the emergency department of Dr. Soetomo General Hospital Surabaya, Indonesia. Thirteen cases were excluded due to incomplete data for statistical analysis, finally there 265 subjects who are eligible for this study. Table I presents the characteristics of cIAI patients in our study with the statistic value. We found that cIAI patients in this study were majority consist of males (65.3%), non-geriatric age (86.4%), patients with normal nutritional status (73.2%), and patient with normal immune status (92%). The average age of our participants was 42.6 years old (median 41±17.5 years).

We found that the ratio of referral and non-referral patients treated in this hospital was almost equal, with 52% of patients are referred from other hospitals. Appendicitis remains the most common cause of cIAI (35.5%), followed by gastroduodenal perforation (21.5%) as the second most common. Most of the cIAI patients had comorbidities (74%). There were 20.4% cases of cIAI with septic shock state. Sixty-one percent (61%) of patients came to our hospital after more than three days from the onset of symptoms appearance (median 3±2.85 days). Medical team usually need 155 minutes (median 150±65 minutes) to undergo a source control surgery in cIAI patient. Those surgery might act as a damage control surgery or as a single-stage definitive surgical procedure. We also found that 71.3% cases of cIAI were classified as a high-risk group based on SOFA scores, where multiple organ failure had occurred.

Statistical analysis for association

A two-stage statistical analysis was conducted in this study to evaluate the association of several patient factors at the time of admission to the hospital with the final outcome. The first stage of statistical test, which used a non-parametric Chi-square, is listed in Table I. There is a significant association ($p<0.05$) between patient factors and mortality during treatment, including age, referral/non-referral case, etiological diagnosis, comorbid disease, septic shock condition, time-to-treatment being longer than 3 days, and high-risk SOFA score.

Second stage of statistical test was carried out to rule out the influence of confounding factors of mortality (Table III). Logistics regression test showed a significant association ($p<0.05$) in several factors, namely age (OR 2.85; 95%CI 1.1–7.3), comorbid disease (OR 7.92; 95%CI 2.05–30.63), condition of septic shock at arrival (OR 5.56; 95%CI 2.40–12.9), Time-to-Treatment being longer than 3 days (OR 2.52; 95%CI 1.24–5.15), and SOFA score more than 2 points (OR 12.14; 95%CI 2.7–54.72).

Table I: Characteristics of participants and Chi-Square Test

Patient's Factors		Outcome		Total	*p* value
		Survived	Not survived		
Gender	Male	115	58	173 (65.3%)	0.577
	Female	58	34	92 (34.7%)	
Age	Non-Geriatric (< 65 years old)	159	70	229 (86.4%)	0.001
	Geriatric (> 65 years old)	14	22	36 (13.6%)	
Referral Case	Non-Referral case	93	33	126 (47.5%)	0.006
	Referral case	80	59	139 (52.5%)	
Etiology Diagnosis	Appendicitis	83	11	94 (35.5%)	0.001
	Gastroduodenal Perforation	30	27	57 (21.5%)	
	Jejunoileal Perforation	21	14	35 (13.2%)	
	Colon Perforation	16	22	38 (14.3%)	
	Hepatic Abscess	6	5	11 (4.2%)	
	Splenic Abscess	2	0	2 (0.8%)	
	Other Intraabdominal Abscess	5	3	8 (3%)	
	Intestine Anastomotic Leakage	3	5	8 (3%)	
	Others	7	5	12 (4.5%)	
Nutritional Status	Overweight	27	15	42 (15.8%)	0.989
	Normal	127	67	194 (73.2%)	
	Underweight	19	10	29 (10.9%)	
Comorbid Disease	No Comorbid Disease	66	3	69 (26%)	0.001
	Comorbid Disease	107	89	196 (74%)	
Septic Shock	No Septic Shock	161	50	211 (79.6%)	0.001
	Septic Shock	12	42	54 (20.4%)	
Immunity Status	Normal	162	82	244 (92.1%)	0,196
	Immunosuppression	11	10	21 (7.9%)	
Duration of Source Control Surgery	< 150 minutes	70	48	118 (44.5%)	0.068
	> 150 minutes	103	44	147 (55.5%)	
Time-to-Treatment	< 3 days	75	28	103 (38.9%)	0,040
	> 3 days	98	64	162 (61.1%)	
SOFA Score	Low Risk (<2)	74	2	76 (28.7%)	0.001
	High Risk (> 2)	99	90	189 (71.3%)	
Total Subjects		**173 (65.3%)**	**92 (34.7%)**	**265**	

Table II: Descriptive analysis of patient's factor

	Age (years)	Surgery Duration (minutes)	Time to Treatment (days)	SOFA score
Mean	42.59	155.19	3.52	3.71
Median	41.00	150.00	3.00	3.00
Std. Deviation	17.536	65.280	2.851	3.114
Minimum value	15	25	0	0
Maximum value	89	420	28	14

Table III: Logistic regression analysis of patient's factor associated with mortality

	Sig. (p)	Odds Ratio	95% CI	
			Lower	Upper
Age >65 years old	**0.030**	**2.846**	**1.109**	**7.306**
Referral case	0.128	-	-	-
Diagnosis	0.102	-	-	-
Nutritional status	0.834	-	-	-
Comorbid disease	**0.003**	**7.921**	**2.048**	**30.631**
Septic shock status	**0.001**	**5.560**	**2.395**	**12.905**
Immunity status	0.881	-	-	-
Duration of source control operation	0.211	-	-	-
Time to treatment	**0.011**	**2.521**	**1.235**	**5.145**
SOFA Score	**0.001**	**12.138**	**2.692**	**54.718**

DISCUSSION

Surabaya is one of the big cities in Indonesia with a population of 1% of national population. This city is the second largest city in Indonesia, following Jakarta as the capital city. Dr. Soetomo General Hospital had surgical emergency visits up to 1.800 cases annually (in 2021) with a bed occupancy rate of 85.47%. The prevalence of cIAI in this hospital is 12% of all surgical emergency cases.[10,11] This prevalence rate is close to the national prevalence rate of cIAI at 10%.[12,13] Therefore, our hospital is considered reliable to represent the characteristics of cIAI in general Indonesian society and along with other condition at the national level.

The statistics of gender, age, and etiological diagnosis found in this study revealed a similar frequency distribution to several previous global studies. CIAOW study in 2013 found that the amount of male patients was higher than female (62.3% : 38.7%). Lalisang et al.5 also found similar findings in Indonesian population with the ratio of 67.3% : 32.7%. Male gender seems to be more susceptible to cIAI compared to women; however, there is no literature that sexplains the rationale of gender as a factor. Majority of cIAI patients was in the non-geriatric age group (< 65 years old), with a median age of 41 years. Llorente et al16 in Spain, Abdel-Kader et al[14], and Inui et al[15] stated that subjects of cIAI patients in their study were between 30 and 50 years old. Perforated appendicitis is the most common cause of cIAI in all research data worldwide. This remains consistent in both developed countries in Europe and developing countries in Asia. As one of the national referral center hospitals, we get many referrals of cIAI cases across the nation for more advanced treatment. Our National Consensus of cIAI recommends that those with a high-risk and complex condition to be referred to a higher-level referral hospital, including ours. This will have an impact on the high number of referral cases for cIAI patients as the participants of our research.[2,4,5,12,14-8]

Comorbid disease, nutritional status, septic shock, and immune status were thought to have an association with mortality in cIAI patients. Llorente et al[16] explained that the proportion of cIAI patients was greater in the group of patients with few and mild comorbidities (Charlson Comorbidity Index/CCI 0-4). Llorente et al16 also mentioned that cIAI patients were predominantly have a normal nutritional status or normal body mass index. Obesity cases were found in 15.8% of cases of our study, comparable to Llorente's study with a frequency of 15.9%. The number of cIAI cases with septic shock in this study was slightly higher than the CIAOW global study, which was 13.1%. The presence of septic shock has been shown to significantly increase the risk of mortality from 5.1% to 36.6% compared with those patients who are clinically stable.[2,16,18]

On average, our participants seek medical treatment on the third day after the onset of symptoms, which according to the literatures are too late to get treated appropriately. Several factors that we found, such as recognition delay, financial/economy issues, and limited access to healthcare facilities in the remote area, were the reasons for the delay in managing patients. Majority of previous studies use the 24-hour time limit as the cut-off value for determining mortality risk. A similar study in our country, Puspitadewi et al[13], revealed only 31.4% cases of patients who came to the healthcare facilities within less than 24 hours since the symptoms onset. However, Llorente et al16 noted that there was >24 hours delay in surgery within 14.8% cases of cIAI.[13,16]

A total of 71.3% cases in our subjects had high SOFA scores on arrival (cut off >2). The presence of organ failure reflects of a life-threatening systemic infection according to the definition of sepsis in the Sepsis-3 criteria. The mortality rate of cIAI patients managed in this study was 34.7%, which is higher than the previous national and global studies. The single centre study of cIAI in Jakarta revealed a mortality rate of 20.9%, other multicentre study in our country showed a

mortality rate of 16.6%, the CIAOW global study in 2014 at 10.5%, while other global study in 2017 at 9.2%. Other literatures state that the mortality rate might actually vary within range of 23-38%.[4,5,7,12,19,20]

The two-stage statistical analysis (Chi-square and Logistic Regression) showed that patient factors such as age, presence of comorbid disease, septic shock condition, delay in time-to-treatment more than 3 days, and SOFA score >2 points were strongly correlated with mortality of cIAI patients during treatment ($p<0.05$). Based on statistics, those five factors, either related or independently associated regardless of their relationship with other factors, were able to affect the final outcome of cIAI patient treated in our hospital. Other factors that have been recorded have no effect on mortality.

Patients who are older than 65 years old are strongly associated with mortality during hospitalization (OR: 2.84; 95%CI 1.11–7.31). This finding is supported by various literatures that conclude that old age is a poor prognosis factor for cIAI patients. Higher risk of mortality in elderly can be explained by the inability of the body to handle stressor. Similarly, they are more susceptible to get sepsis and multiple organ failure due to the declining physiological function and disability to deal with stress. According to various scoring systems, age is considered as one of the poor prognostic factors in cIAI patients, although the age limit varies greatly within studies. The Manheimm Peritoneal Index (MPI) scoring system, WSES Sepsis Severity Score, and Calgary PIRO score are prognostic scoring systems for cIAI that utilize age with different cut-off point, where the patient's age is inversely correlated with the patient's survival.[16,17,21,22]

The presence of comorbid disease also increases the risk of mortality (OR: 7.92; 95% CI 2.05–30.63). Llorente et al[16] stated that the presence of comorbid disease affects the incidence of morbidity and mortality in cIAI patients significantly up to 90 days after infection. Comorbid diseases influence the occurrence of complications based on the Clavien-Dindo index. Comorbid disease should be measured by the Charlson Comorbidity Index (CCI) to predict its relationship with morbidity and mortality in cIAI patients. Up to 90 days of treatment, the greater the CCI value, the higher the rate of mortality and the Clavien Dindo's morbidity index. One of the limitations of this study is that we do not use CCI index system in assessing the presence of comorbid disease in patients, thereby the association analysis of comorbid disease cannot be carried out. This study also does not classify the types of comorbid diseases that affect mortality.[16]

The incidence of septic shock at the time of diagnosis is significantly associated with patient mortality during treatment (OR: 5.56; 95%CI 2.40–12.91). Similarly, Luo et al23 stated that the incidence of septic shock affected patient mortality up to 28 days of treatment in cIAI patients ($p<0.001$; OR 5.69 95%CI 3.31–9.77). Septic shock defined as a condition of cardiovascular organ failure characterized by the need for vasopressors to maintain arterial pressure above 65 mmHg accompanied by an elevated lactate levels above 2 mmol/L. This circumstance will have a consequence on peripheral tissues with significant hypoxia in the form of oxidative stress. The mortality rate in our patients with septic shock was quite high (77%), in contrast to Luo et al23 at 30.9%.[23] Patients with septic shock are usually failed to survive in late phase of intensive care. Literature explain that early death was secondary to the irreversible multiorgan failure associated with the underlying infection (82%) and the presence of mesenteric ischemia (6.4%). In the late phase, death mostly happened after a family decision to halt the treatment (29%) and the presence of nosocomial infection (20.4%).[24]

The duration of time from onset to treatment in patients are significantly influence the mortality of cIAI patients. There are a total of 61.1% of patients who seek for medical treatment after the third day of symptoms onset. The longer the time for patient to get treated, the lower the chance their survival (OR 2.52 with 95% CI 1.24–5.15). Several studies use a lower cut-off value of 24 hours for the treatment of cIAI. Delay in source control surgery is a major risk factor for patient mortality. The patient's survival rate is significantly decreased when the source control surgery is performed in more than 6–8 hours. Global experts suggest that source control surgery should be carried out as early as possible. However, there is currently no agreement on the exact time limit to carry out the surgery. Early surgery and adequate resuscitation are both critical factors that surgeons must consider to lower the morbidity and mortality rate. Major surgical procedures including intestinal resection or only percutaneous drainage under local anesthesia both can be performed in critically ill patients. Minimal interventions are still recommended to treat sepsis in critically ill patients. Delay of treatment in this study was influenced by several things, including patient knowledge, limited access to healthcare facilities, limited medical support, and other non-technical factors.[16,23,25]

Assessment of SOFA scores on arrival had a predictive value on patient mortality (OR: 12.14; 95%CI 2.69–54.72). SOFA score can be measured in cIAI patients who fall into a critical condition. This score can be applied in the intensive care unit for both non-surgical and surgical critical patients. Creatinine levels and level of consciousness by the Glasgow Comma Scale are both the strongest prognostic factors associated to the patient mortality. Despite the fact that there are various scoring systems recently in the assessment of mortality specifically for cIAI patients, SOFA score remains an accurate, easy-to-use, and objective tool for assessing patient's severity.[26,27]

Prolonged duration of source control surgery may result in poor survival rate, secondary to the declining immune defense mechanisms which lead to several morbidities. Immunosuppression conditions and delayed detection will also make the patient's condition worse.[28] There is no doubt that widespread infections in the bloodstream can raise morbidity and mortality by up to 31%. In addition, the duration of treatment and health costs will increase significantly.[29] The concept of adequate damage control surgery has been routinely applied to cIAI cases that are previously thought to have a high mortality risk. As has been discussed, understanding the risk factors of mortality may promote surgeons to perform simple procedure such as bedside percutaneous drainage in critically ill patients.[30]

Following a 48-hour period in which the patient's condition has improved, definitive surgery may be considered. When a one-step definitive management strategy is implemented right away in severe and critical cases, a high risk of mortality will increase.[5]

CONCLUSION

Several patient factors on arrival which are significantly associated with the incidence of mortality during treatment in the cIAI patients are being older than 65 years, presence of comorbid disease, septic shock, Time-to-Treatment longer than 3 days, and SOFA score higher than 2 points. This finding is consistent with the previous scientific literature as a predictor of mortality in the management of cIAI patients.

There are several limitations in this research. We did not collect microbiologic and antibiotic susceptibility data which also may affects the prognosis regarding source control management. We did not use the Charlson Comorbidity Index (CCI) to assess comorbid disease in our patients. This study did not analyze the confounding factors during patient care, such as the use supportive vasoconstrictor therapy during septic shock, use of ventilator as a respiratory support, perioperative fluid therapy, etc. Morbidity assessment using Clavien Dindo index may be carried out to assess its association within cIAI after the patient is discharged. Apart from the above description, patient mortality can also be predicted through other methods, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, procalcitonin levels, and the Neutrophil-Lymphocyte ratio.[31]

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest and financial in the writing of this manuscript.

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ETHICAL CLEARANCE

This study was reviewed and approved by the Medical Ethical Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (Ref. No.: 0956/LOE/301.4.2/VII/2022) following the guidelines of the Declaration of Helsinki.

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