Predictive factors of mortality in patients with acute mesenteric ischemia.

A retrospective study

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Predictive factors of mortality in patients with acute mesenteric ischemia. A retrospective study.

AIM: *The aim of this retrospective study was to evaluate the impact of some risk factors on mortality in patients with Acute mesenteric ischemia (AMI).*
MATERIALS AND METHODS: *From September 2003 to August 2011, 200 patients were operated on for bowel infarction at our unit: 149 were included in the study. For each patient, socio-demographic (gender and age) and clinical data (extent of necrosis, predisposing factors, WBC, LDH, comorbidities) were collected from patients' clinical records.*
RESULTS: *Of the 149 patients who underwent surgery, 57 (38.3%) died. A significantly higher mortality was associated with older age (79.9 versus 74.2 years, $p < 0.01$), higher LDH serum levels (695 versus 636 UI/L, $p < 0.01$), higher WBC (25.1 versus 22.5 X $10^3/mm^3$; $p < 0.01$), and extent of necrosis ($p< 0.01$). Otherwise, there was no correlation between comorbidities and mortality. Finally, multivariate analysis confirmed the significantly higher risk of death in patients with right colon and massive small bowel infarction (adjOR= 3.58; 95% CI=1.36-9.42) and intestinal perforation (adjOR=31.1; 95% CI=2.45-395.7).*
DISCUSSION: *The results of our study suggest that the contribution of laboratory tests is limited, even if increased indexes of necrosis (such as LDH) associated with neutrophilic leukocytosis and metabolic acidosis, may help in defining diagnosis/prognosis, though with* low accuracy.
CONCLUSIONS: *The extent of necrosis and diagnostic delay seem to be the most important prognostic factors even after adjusting for confounding due to age, presence of comorbidities, and laboratory tests (LDH and WBC).*

KEY WORDS: Acute mesenteric ischemia, Mortality, Predictive factors

Introduction

Acute mesenteric ischemia (AMI) accounts for approximately 1% of all causes of acute abdomen, and is associated with very poor prognosis. The morality rate is between 59% and 93% [1,9].

Incidence increases from the sixth to eighth decade of life, with a slight prevalence in males. The risk of developing bowel infarction is significantly higher in patients with a history of atrial fibrillation and/or myocardial infarction, in smokers, and in patients suffering from hypertension [2]. Abdominal aortic aneurysm is another important risk factor [10].
The general factors affecting the prognosis seem to be advanced age (> 75 years), extent of necrosis, and recent major cardiovascular surgery [7,11]. The etiology is embolic or thrombotic arterial occlusion in 60-70% of cases[12], non-occlusive ischemia and infarction in 20-30%, and mesenteric venous thrombosis in 5-10% [13].

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Multislice computed tomography is a rapid and noninvasive technique that is being increasingly employed for the early diagnosis of AMI in the emergency unit [14].
Evidence from the literature shows that one of the factors that contribute to the high mortality rate is the fact that there is no sensitive and specific laboratory test for an early diagnosis of bowel infarction, and the diagnosis is often delayed [1,10,15]. Measurement of the serum enzyme system may offer important clues for a diagnosis. [10].
The aim of this study was to evaluate two discrete aspects of the disease: first, the role of lactic dehydrogenase (LDH) and white blood cell count (WBC) in the diagnosis, and, second, the impact of some risk factors on a *quoad vitam* prognosis in a series of patients with bowel infarction requiring resection.

Materials and Methods

From September 2003 to August 2010, 200 patients (95 women, 105 men) with bowel infarctions were observed at the Unit of General and Emergency Surgery of the P. Giaccone Policlinico Hospital, in Palermo, Italy. All patients underwent intestinal resection according to the extent of necrosis. No patient was a candidate for conservative treatment (revascularization) because of the late diagnosis and advanced disease [11]. Thus, there only were cases of overt necrosis. The patients' average age was 76.4 years, ranging between 36 and 94 years. Nine patients were excluded because of massive ischemic necrosis of stomach, bowel, colon, liver or spleen during surgical exploration, and died during or immediately after surgery because no potentially effective treatment was feasible.
Moreover, 42 cardiac surgery patients were also excluded from the study since they had non-occlusive mesenteric ischemia [16], as confirmed during surgical exploration. The final cohort was composed of 149 patients. Often, abdominal x-ray was done in the presence of signs of acute abdomen of uncertain origin. The most frequent signs were reduction or absence of colonic gasification, multiple air fluid levels, and distension of the small bowel and right colon. Ultrasonography sometimes showed free fluid in abdomen, but did not prove useful for a diagnosis. Multislice computed tomography (CT) without contrast enhancement was done in 109 patients, contrast-enhanced CT was done in 40.
In addition to gender and age, we collected the following data for each patient: extent of necrosis (categorized as segmental; massive of small bowel, small bowel + right colon, left colon); comorbidities (hypertension, diabetes mellitus, ischemic cardiomyopathy, valvular disease, aortic aneurysm, renal failure, portal hypertension); time between diagnosis and treatment; leukocytosis (white blood cells [WBC] $*10^3/mm^3$); and serum lactate dehydrogenase (LDH) (as UI/mL).
Leukocytosis was found in all patients at admission, and ranged from 13.5 to 41 x 10 ^ 3/mL WBC, in agreement with the literature. (11,15,16) Additionally, a significant increase in LDH was detected in about 70% of the patients, again in accordance with the findings of some studies [10,17].
With the aim of evaluating the delay between onset of the disease and diagnosis, the patients were classified in four different stages identified by diagnostic signs of reference (laboratory tests/suffering of wall/abdominal fluid/gas). According to signs of disease progression and, therefore, according to the diagnostic delay, we divided the patients into the four following groups: Group 1: clinical signs + laboratory tests; Group 2: suffering of wall; Group 3: abdominal fluid; and Group 4: gas, which is the stage that already implies intestinal perforation.

TABLE I - *Characteristics of the 149 Patients Enrolled in the Study*

	N=149
Age in years, mean (SD)	76.4 (12.6)
White blood cells/mm^3, mean (SD)	23,509 (5,886)
Lactate dehydrogenase UI/L, mean (SD)	658.5 (134.9)
Type of intestinal ischemia, number (%)	
segmental bowel ischemia	11 (7.4)
massive small bowel infarction	65 (43.6)
left colon infarction	29 (19.5)
right colon + massive small bowel infarction	44 (29.5)
Diagnostic delay, number (%)	
Group 1	6 (4)
Group 2	25 (16.8)
Group 3	89 (59.7)
Group 4	29 (19.5)
Diabetes, number (%)	
Yes	82 (55)
No	67 (45)
Hypertension, number (%)	
Yes	96 (64.4)
No	53 (35.6)
Aortic aneurysm, number (%)	
Yes	16 (10.7)
No	133 (89.3)
Chronic renal failure, number (%)	
Yes	25 (16.8)
No	124 (83.2)
Portal hypertension, number (%)	
Yes	12 (8.1)
No	137 (91.9)
Ischemic cardiomyopathy, number (%)	
Yes	26 (17.4)
No	123 (82.6)
Cardiac valvulopathy, number (%)	
Yes	6 (4)
No	143 (96)

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Statistical Analysis

All collected data were entered in a database created with Excel 2007. Absolute and relative frequencies were calculated for qualitative variables, while quantitative variables were summarized as mean ± standard deviation, median (interquartile range). Categorical variables were analyzed using a chi-square test (Mantel-Haenszel) or Fisher's exact test. For quantitative variables the normal distribution was verified by the Shapiro-Wilk test for normality. Mean ± standard deviation data were compared with the Student t-test. Odds ratios (OR) and 95% confidence intervals (CI) were computed using unconditional logistic regression. All variables showing a statistically significant association ($p<0.05$) with mortality were considered for inclusion in a backward stepwise logistic-regression analysis. Measures of goodness of fit were calculated to compare logistic regression models by using Akaike's information criterion (AIC), and the model with the lowest AIC was considered the best fit. All data were analyzed using the R statistical software package.

Results

The characteristics of the 149 patients enrolled in the study are reported in Table I. Table II shows the univariate analysis of patient characteristics for deceased versus surviving patients. Older age, increased WBC and LDH levels, type of intestinal ischemia, diagnostic delay, and presence of aortic aneurysm were significantly associated with patient mortality. Otherwise, WBC and LDH levels were not associated with type of intestinal ischemia (Fig. 1).

Finally, as shown in Table III, multivariate analysis confirmed the significantly higher risk of death in patients

Table II - *Univariate analysis of characteristics of deceased versus surviving patients.*

	Deceased patients (N=57)	Surviving patients (N=92)	p-value
Age in years, mean (SD)	79.9 (9.2)	74.2 (13.9)	<0.01
White blood cells*10^3/mm^3, mean (SD)	25,123 (56,725)	22,509 (5,086)	<0.01
Lactate dehydrogenase UI/L, mean (SD)	694.8 (135.3)	635.9 (130.4)	<0.01
Type of intestinal ischemia, number (%)			
segmental bowel ischemia	0 (0)	11 (100)	<0.01
massive small bowel ischemia	21 (32.3)	44 (67.7)	
right colon and massive small bowel infarction	24 (54.5)	20 (45.5)	
left colon infarction	12 (41.2)	17 (58.6)	
Diagnostic delay, number 25 (%)			
Group 1	1 (16.7)	5 (83.3)	<0.01
Group 2	2 (8)	23 (92)	
Group 3	29 (32.6)	60 (67.4)	
Group 4	4 (13.8)	(86.2)	
Diabetes, number (%)			
Yes	35 (42.7)	47 (57.3)	0.29
No	22 (32.8)	45 (67.2)	
Hypertension, number (%)			
Yes	40 (41.7)	56 (58.3)	0.33
No	17 (32.1)	36 (67.9)	
Aortic aneurysm, number (%)			
Yes	11 (68.8)	5 (31.3)	0.02
No	46 (34.6)	87 (65.4)	
Chronic renal failure, number (%)			
Yes	45 (36.3)	79 (63.7)	0.38
No	12 (48)	13 (52)	
Portal hypertension, number (%)			
Yes	3 (25)	9 (75)	0.50
No	54 (39.4)	83 (60.6)	
Ischemic cardiomyopathy, number (%)			
Yes	13 (50)	13 (50)	0.26
No	44 (35.8)	79 (64.2)	
Cardiac valvulopathy, number (%)			
Yes	0 (0)	6 (100)	0.12
No	57 (39.9)	86 (60.1)	

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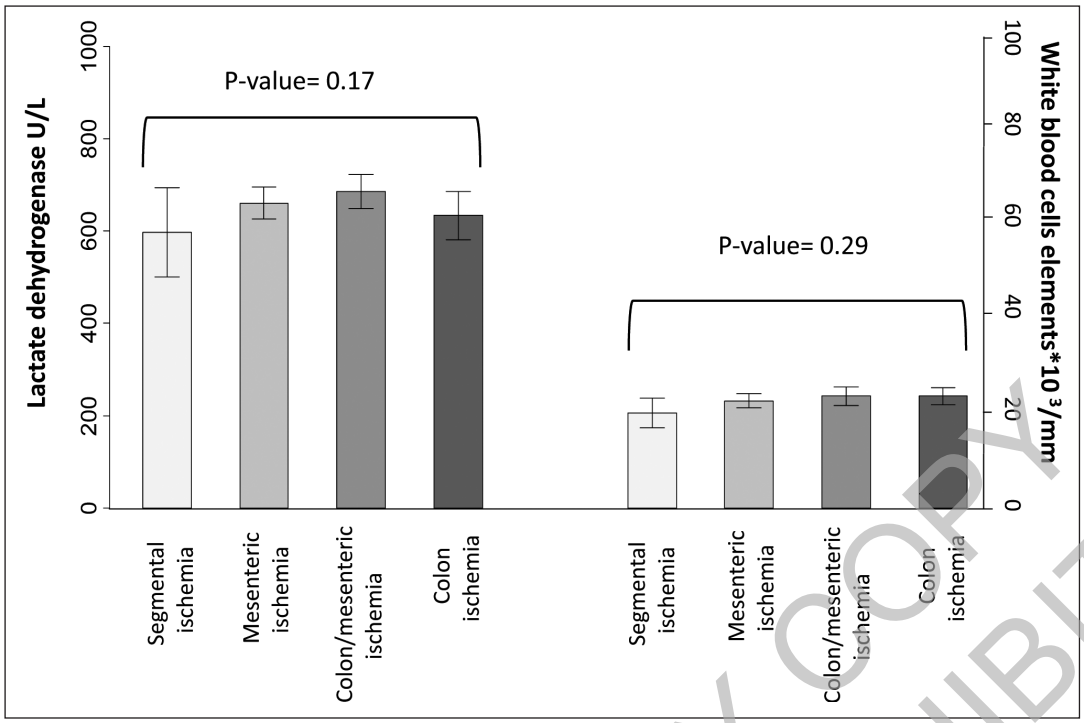

Fig. 1: LDH and WBC as predictors of the type of intestinal ischemia

TABLE III - *Logistic regression analysis of factors associated with patient mortality.*

	Adjusted OR (95% CI)	Adjusted p-value
Age in years, mean (SD)	1.02 (0.98-1-06)	0.31
White blood cells*10^3/mm^3, mean (SD)	1.02 (0.94-1.1)	0.69
Lactate dehydrogenase UI/L, mean (SD)	1.01 (0.99-1.011)	0.20
Type of intestinal ischemia, number (%)		
segmental bowel ischemia or massive small bowel ischemia	referent	
right colon and massive small bowel infarction	3.58 (1.36-9.42)	0.01
left colon infarction	2.16 (0.7-6.61)	0.18
Diagnostic delay, number (%)		
Group 1	referent	
Group 2	0.56 (0.04-8.5)	0.67
Group 3	2.73 (0.26-28.5)	0.40
Group 4	31.12 (2.45-395.7)	0.008
Aortic aneurysm, number (%)		
No	referent	
Yes	2.64 (0.63-11.1)	0.18

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with right colon and massive small bowel infarction (adjOR=3.58; 95% CI=1.36-9.42) and intestinal perforation (adjOR=31.1; 95% CI=2.45-395.7).

Discussion

The peculiar pathophysiological changes in acute intestinal ischemia are systemic inflammatory response syndrome, bacterial translocation and reperfusion injury. These conditions, provoking damage in intestinal microcirculation, exacerbate tissue ischemia. The increased capillary permeability, as a response to inflammation, and the destruction of the mucosal barrier induce bacterial translocation [17-19]. Multi-organ failure with hepatic, cardiac and pulmonary involvement may appear in the final stage [3]. Mucosal damage and increased capillary permeability are found in the areas where the necrosis is incomplete (i.e, primarily in non-occlusive ischemia) [29]. This is a result of the restoration of circulation, which prompts

the release of free radicals, with subsequent damage to the intestinal wall [18].

The progression to advanced clinical and pathological stages (peritonitis, perforation) dramatically reduces life expectancy [15]. Thus the extreme seriousness of intestinal infarction must be constantly stressed, since its insidious clinical features can delay diagnosis. In most cases, such information as patient history, clinical examination, laboratory tests, and CT scan signs have to be examined in order to arrive at a correct diagnosis.

The results of our study suggest that the contribution of laboratory tests is limited, even if increased indexes of necrosis (such as LDH) associated with neutrophilic leukocytosis and metabolic acidosis, may help in defining diagnosis/prognosis, though with low accuracy [21]. In this sense, LDH and WBC have not been associated with the extent of necrosis or, on multivariate analysis, patient mortality.

Even instrumental tests seem to be limited. According to the literature [3,4] diagnosis tests such as ultrasound and abdominal x-ray have shown little specificity in the diagnosis of acute mesenteric ischemia. However, the detection of air levels can play a very important role in arriving at a *quoad vitam* prognosis and, indeed, in our patients, were correlated with an excess of mortality risk. Mortality was also associated with right colon and massive small bowel infarction. As a consequence, the importance of an early diagnosis should be stressed, since late diagnosis often does not allow for a full bowel recovery, and, once necrosis appears, it precludes acceptable results, thus triggering multiple organ failure. Overall survival was significantly better in patients with a segmental necrosis or a necrosis limited to the small bowel.

We found no correlation with associated diseases (diabetes mellitus, hypertension, aortic aneurysm, chronic renal failure, portal hypertension, ischemic cardiomyopathy, heart valve diseases).

Conclusion

The extent of necrosis and delay in diagnosis seem to be the most important prognostic factors, even after adjusting for confounding due to age, presence of comorbidities and laboratory tests (LDH and WBC). We believe that the keys to increased survival should be considered an early diagnosis [1] and timely surgery [3].

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Riassunto

Scopo del presente studio retrospettivo è valutare l'impatto di alcuni fattori di rischio sulla mortalità dell'ischemia mesenterica acuta (AMI).

149 pazienti giunti alla nostra osservazione dal settembre 2003 all'agosto 2011 sono stati reclutati per lo studio. Per ciascun paziente, sono stati rilevati, dalle cartelle cliniche, età, sesso, dati clinici (estensione della necrosi, fattori predisponenti, conta globuli bianchi, valori di LDH, comorbosità). La mortalità complessiva del campione è risultata del 38,3%. Un'associazione statisticamente significativa è risultata tra questa ed età avanzata (79,9 vs. 74,2; p<0,01), elevati livelli sierici di LDH (695 vs. 636 UI/l), elevata leucocitosi neutrofila (25100 vs. 22500 GB; p<0,01) ed estensione della necrosi (p<0,01). Peraltro, non è stata trovata associazione tra comorbosità e mortalità. Infine, l'analisi multivariata ha dimostrato un elevato rischio di mortalità nei pazienti con necrosi massiva del piccolo intestino, ancor più se associata ad interessamento del colon dx. (adj OR = 3,58; 95% CI = 2.45-395.7).

I risultati dello studio suggeriscono un limitato apporto diagnostico e prognostico degli esami di laboratorio, anche se l'associazione di marcato incremento degli indici di necrosi (LDH), leucocitosi neutrofila ed acidosi metabolica, possono contribuire a definire la diagnosi e la prognosi, sebbene con una limitata accuratezza. L'estensione della necrosi ed il ritardo diagnostico sembrano essere i più importanti fattori prognostici, anche dopo correzione per età, comorbosità e dati di laboratorio (LDH e WBC).

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