



UNIVERSITA' DEGLI STUDI DI GENOVA
Dipartimento di Medicina Interna e Specialità Mediche (DIMI)

Dottorato di Ricerca in
“MEDICINA INTERNA CLINICO-SPERIMENTALE” (XXX° ciclo)

Curriculum
“Malattie dell’apparato digerente e del fegato”
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**ACUTE MESENTERIC ISCHEMIA
IN THE EMERGENCY DEPARTMENT:
A RETROSPECTIVE ANALYSIS TO DEVELOP A
CLINICAL DIAGNOSTIC TOOL AND A
PROSPECTIVE VALIDATION STUDY
SUPPORTED BY DUPLEX ULTRASOUND**

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INTRODUCTION: A BRIEF OVERVIEW ABOUT ACUTE MESENTERIC ISCHEMIA

Acute Mesenteric Ischemia (AMI) is a condition due to inadequate blood flow support and oxygen delivery to meet the metabolic demands of the visceral organs resulting in ischemia and eventually gangrene of the bowel wall. Although considered relative rare, it is a potentially life-threatening condition if not early identified and properly treated.

EPIDEMIOLOGY

Among hospital admissions for abdominal pain, overall AMI prevalence is attested around 0,1%.¹ However it may increase exponentially in elderly and people with risk factors and comorbidities for cardiovascular disease.^{2,3} In a population-based study in Sweden, Acosta et al. found an exponential increase of AMI incidence

with age reaching a peak of 217 per 100,000 person years in the age category of 85 and above.⁴

Aetiological distribution has reported to be 60-70% for occlusive mesenteric ischemia (OMI), 20-30% for non occlusive mesenteric ischemia (NOMI), 10-18% for venous mesenteric thrombosis, 2-3% other causes. (see Figure 1)⁵

No clear gender predominance has been found and male-to-female ratio for AMI varies widely among population-based studies.^{6,7}

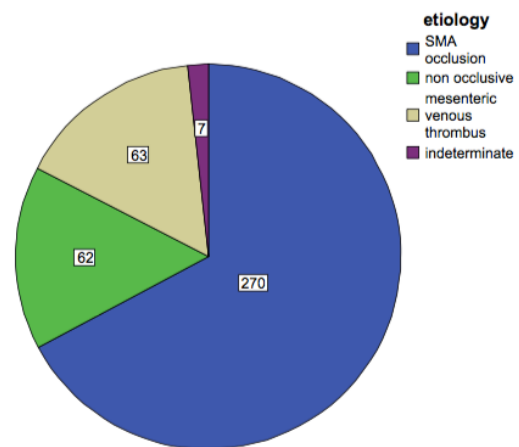


Figure 1 Distribution of etiologies in patients with acute mesenteric ischemia in Malmö, Sweden between 1970 and 1982, when autopsy rate was 87%. SMA, superior mesenteric artery.⁵

A matter of concern for a so rare disease is the high mortality rate attested around 60-90%.^{8,9} It seems to be related not only to the intrinsic severity of the ischemic damage to gut mucosae, but also to a delayed diagnosis due to a non-specific clinical presentation and a “watch and see” approach in elderly with abdominal pain.^{10,11}

ANATOMICAL INSIGHT

The knowledge of the mesenteric circulation is essential to understand the physiopathological implications of acute mesenteric ischemia.

Three are the main arterial vessels that supply foregut, midgut and hindgut: the celiac axis, the superior mesenteric artery (SMA), and the inferior mesenteric artery (IMA) respectively.

The celiac axis arises from the ventral surface of the aorta at the T12-L1 vertebral body. It courses antero-inferiorly before branching into the common hepatic, splenic, and left gastric arteries. Many possible variations are described.¹²

The SMA comes off the ventral aorta and supplies the midgut by giving off the inferior pancreaticoduodenal artery, middle colic, right colic, and jejunal and ileal branches.

The inferior mesenteric artery (IMA) arises from the aorta at L3-L4 level. The first branch is the left colic artery. There are multiple other smaller branches of the artery that give off descending colic and sigmoid branches. The superior rectal artery is the terminal branch and has right and left branches.¹³

The interconnection between these vessels is made of many collateral vessels and anastomosis, most of which are functional thus activated in case of necessity (for example poor blood supply). The main are:

- The pancreato-duodenal arcade connects the celiac axis (superior pancreaticoduodenal arcade) to the superior mesenteric artery (inferior pancreaticoduodenal arcade);
- The dorsal pancreatic artery that has its origin from the SMA is important in collateral circulation between the SMA and celiac axis;
- The Arc of Buhler connects the celiac axis and SMA vertically and ventral to the aorta;
- The Arc of Barkow also connects the celiac axis and SMA through an anastomosis of the right gastroepiploic artery and left gastroepiploic artery. It assists in supplying the transverse colon;
- The Marginal artery of Drummond connects the SMA and IMA. This collateral vessel is formed by the terminal branches from the SMA (ileocolic artery, right colic artery, left colic artery) and the IMA (left colic artery and sigmoid arteries);
- The Arc of Riolan, also known as the mesenteric meandering artery, also connects the SMA and IMA. The classic collateral pathway of this vessel connects the middle colic artery to the left colic artery

Finally the superior rectal artery, which is a branch of the IMA, and the inferior rectal artery, which is a branch of the internal iliac arteries, may provide collaterals between these two circulatory pathways.¹⁴

PATHOPHYSIOLOGY

As mentioned above, AMI is due to an impairment between blood supply and gut tissue demands. This condition is the result of an obstruction or diminished blood support of the arterial system or an outflow reduction of the mesenteric veins system.¹⁵

When oxygen delivery and extraction capacities is below tissue demands, the ischemic injury of the visceral organs determines local and systemic inflammatory pathways.¹⁶ Vasodilatation, due mainly to inducible nitric oxide release, is the first response, but prolonged ischemia leads to inflammatory cells activation producing cytokines, platelet activating factors, leukotriene and toxic free oxygen radicals.^{17,18} Leukocyte adhesion, platelet aggregation and nitric oxide increase the damage of the intestinal microcirculation.¹⁹ Toxic free oxygen radicals, that damage the cell membrane through lipid peroxidation, cause an increase in capillary permeability.²⁰ Progressive interstitial imbibition reduces oxygen extraction from blood flow and causes vasoconstriction that can be maintained even after intestinal blood flow returns to normal.²¹ Intestinal mucosa and sub-mucosa are the first target of this insult resulting in a reduced capacity to prevent bacterial translocation from bowel lumen to systemic blood flow.²² Consequently, if not reversed, ischemic insult may lead to full-thickness injury, infarction and then necrosis of the bowel. Furthermore systemic bacteremia and septic state is established causing multi-organ failure and death.²³

Collateral vessels and anastomosis can be activated but it may take several days or weeks. Thus in case of slowly progressing mesenteric atherosclerosis they can be already fully developed and provide a source of blood supply even in case of

thrombotic stenosis. Conversely, in case of abrupt arterial occlusion such as caused by emboli, collateral vessels are useless in the first hours so that they cannot prevent ischemic insult to gut tissue.²⁴

CLASSIFICATION AND CLINICAL PRESENTATION

AMI is classified as: Occlusive Mesenteric Ischemia (OMI) that is result of an acute arterial vessel occlusion due to thrombosis or embolus; Non-Occlusive Mesenteric Ischemia (NOMI) caused by reduced arterial blood support due to reduced cardiac output, shock state or arteriolar vasoconstriction of the mesenteric vessels itself without stenosis of the main artery; Mesenteric Venous Thrombosis (MVT) caused by venous thrombosis causing outflow impairment and increase of the capillaries pressure. An non-acute form is called Chronic Mesenteric Ischemia (CMI) or Ischemic colitis (IC) due to progressive arterial atherosclerosis that is the cause of abdominal angina.

Occlusive Mesenteric Ischemia (OMI)

Arterial obstruction is considered the most common cause of mesenteric ischemia.

Embolic occlusion is attested around 40-50% of cases whilst thrombotic occlusion of a previously stenotic mesenteric vessel around 20-35%.

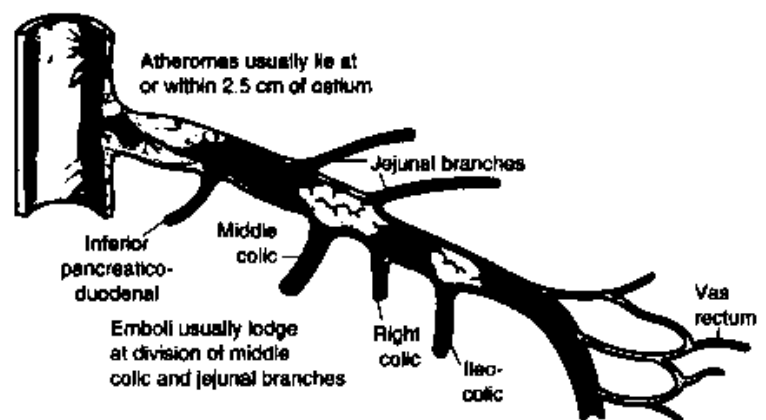


Figure 2 Principal sites of occlusion of the superior mesenteric artery

Other causes, such as artery dissection or vasculitis, represent less than 5% of cases.²⁵

The most common embolic source is from the heart and atrial fibrillation, valvular disease or prior myocardial infarction are commonly seen in these patients.²⁶ The embolus may occlude the arterial lumen completely or partially. Emboli tend to lodge at points of normal anatomical narrowing, usually immediately distal to the origin of a major branch. Typically, the embolus lodges a few centimeters distal to the origin of the SMA, sparing the proximal jejunal branches, and allowing preservation of the proximal jejunum. (see Figure 2) Clinically this condition is characterized by an abrupt onset of severe abdominal pain “out of proportion to clinical signs”, sometimes associated with diarrhea and/or hematochezia. Most part of the small bowel and right-side of the colon suffers from severe ischemia and usually the treatment is bowel resection of the ischemic segment.²⁷

Thrombotic stenosis and occlusion of the arterial mesenteric vessels is responsible for approximately 25% of AMI cases. Superior mesenteric artery is the most involved vessel in atherosclerotic plaque formation and stenosis, often at its origin. Thus ischemia usually develops from proximal jejunum to mid transverse colon. Narrowing of the SMA has the greatest impact on the development of mesenteric ischemia.²⁸ Celiac axis and inferior mesenteric artery are less involved, probably for their different angle origin from the aorta. Collateral vessels may be present, consistent with an acute worsening of an underlying chronic condition. This condition determines a less abrupt onset of thrombotic AMI than embolic AMI.²⁹

More than 90% of cases of chronic mesenteric ischemia are related to progressive atherosclerotic disease that affects the origins of the visceral vessels. Some of these patients may have a known atherosclerosis involvement in other vascular district and risk factors for cardiovascular events.³⁰

Non-Occlusive Mesenteric Ischemia (NOMI)

Non-occlusive mesenteric ischemia is approximately responsible for 20-30% of AMI cases. This condition is typically the result of a prolonged state of hypotension due to low cardiac output and/or shock states. In order to preserve vital organ perfusion, blood flow is redistributed through arteriolar mesenteric vessels vasoconstriction causing severe intestinal hypoperfusion despite the mesenteric arteries being patent.^{31,32} Furthermore vasoactive drugs, inotropes, digoxin and beta blocker have been associated with arteriolar vasoconstriction.^{33,34} The diagnosis of NOMI can be extremely challenging as symptoms are subtle and non-specific. Critically ill patients such as those mechanically ventilated and/or post-operative from major surgery (especially cardiac or aortic surgery) are more predispose to develop this condition.

Mesenteric Venous Thrombosis (MVT)

Mesenteric venous thrombosis accounts for 10-18% of all AMI cases with an incidence of 2.7 per 100.000 person-years. However its prevalence has increased over the last decades.³⁵ When a thrombotic event of the porto-mesenteric circulation occurs, the venous return from the bowel is compromised resulting in mesenteric venous hypertension. The outflow impairment will lead to bowel wall ischemia, further worsened by a reactive arterial spasm, and full thickness bowel wall damage.³⁶ Predisposing factors to MVT are cirrhosis, hypercoagulable states, local anatomical alteration that may contribute to venous outflow impairment.³⁷ Clinically, acute mesenteric venous thrombosis is characterized by acute onset of

abdominal pain within 24-72 hours even though in 10-15% of cases a more subtle presentation is described with non-specific symptoms.³⁸

DIAGNOSTIC WORKUP

A critical concept is that AMI diagnosis should be driven by “clinical suspicion” and everything should be done as soon as possible to confirm or rule out the diagnosis.

Laboratory Tests

Laboratory tests are of little help in the diagnosis of AMI as no specific biomarkers for bowel ischemia has been found.³⁹

Patients with AMI have been found having leucocytosis, metabolic acidosis, elevated acid lactate and D-dimer but none of them seem too specific.⁴⁰ About the latter, for its high negative predictive value, Acosta et. al suggested that it may be used as an exclusion test only if arterial occlusion is unlikely.⁴¹ Over the past decades, new biomarkers such as alpha-glutathione S-transferase (GST) and intestinal plasma fatty acid-binding proteins (FABPs) were also investigated. GST and FABPs sensitivity for AMI ranged from 20% to 100% and from 64% to 100% respectively but they are not so widespread among Emergency setting.^{42,43}

Imaging

Nowadays, multi detector computed tomography (MDCT) of the abdomen with contrast enhancement for arterial and venous phase (CTA), has become the test of choice to investigate AMI replacing conventional angiography.⁴⁴ Both arterial occlusion and venous thrombosis can be evaluated as well as bowel wall ischemic insult. It's sensitivity and specificity are attested around 90-97% and 93-97% respectively.⁴⁵ Furthermore its diagnostic accuracy can be improved if the

radiologist is aware about the clinical suspicion of AMI as some of the signs are subtle and can be overlooked.^{46,47} Decreased or absent bowel wall enhancement and pneumatosis are probably the most specific CT signs of AMI even if effected by poor sensitivity (16-62%).⁴⁸ Conversely other signs like bowel wall thickening, mesenteric fat stranding, luminal dilatation are more commonly present but less specific. One of the main limitation of this technique is the necessity of contrast enhancement, if not used the diagnostic accuracy is far less and can even increase AMI mortality.⁴⁹ Finally the risk related to radiation exposure has to be considered.⁵⁰



Catheter-based arteriography maintains the role of the gold-standard in diagnosing overall arterial occlusion. Anyway, for its invasive nature, it is considered a second level diagnostic test after CTA. Other than diagnostic feature, it can support, when indicated, endovascular intervention and treatment. ⁵¹

The role of other imaging diagnostic technique is limited: abdomen X-ray is poorly sensible and if AMI signs are present (pneumatosis, pneumobilia, perforation) the ischemic damage is well established with little chance to revert it; magnetic resonance with Gadolinium contrast enhancement is able to detect vessels occlusion but with less accuracy than CT-A and the longer execution time and availability reduce its utilization in acute setting. ^{52,53}



TREATMENT: A “TIME DEPENDENT” APPROACH

Treatment strategies differ on the basis of etiological category, thus is important to properly identify the type of AMI. Furthermore it is important to establish whether transmural bowel necrosis has already occurred and if signs of peritonitis are present.

An emerging concept is that the soon AMI is confirmed and properly treated, the better is the outcome.^{9,54,55} Like all others vascular ischemic disease, there's a continuum from vascular occlusion/stenosis, reduced blood flow, an early phase of tissue reversible insult and finally, if not resolved, irreversible damage and necrosis will be established. In recent years, studies reported a reduction in mortality to less than 30% when treatment is begun within 6-8 hours after symptoms onset, thus AMI can be considered a time-dependent disease.^{56,57}

Therapeutic Strategies for OMI

In hemodynamically stable patients and without signs of peritonitis, after CTA confirmation of OMI, endovascular therapy should be attempted before revascularization as the primary revascularization method.⁵⁸ The aim of this technique is aspiration thrombectomy in case of emboli or stent application in case of atherosclerotic occlusion. Another viable option in case of incomplete thrombus aspiration or distal embolization is catheter directed thrombolysis, usually with recombinant tissue plasminogen activator.⁵⁹ Nowadays aspiration thrombectomy is considered the method of choice because reperfusion can be achieved quicker than thrombolytic agent infusion.⁶⁰ If endovascular approach is unsuccessful or unfeasible, open surgical embolectomy or vascular bypass is the alternative.⁶¹

In case of CTA findings of transmural bowel damage, clinical signs of peritonitis along with metabolic acidosis and severe hyperlactatemia, reflection of a prolonged state of ischemia, then open laparoscopy for extensive bowel resection become the first line approach.⁶²

Therapeutic Strategies for NOMI

As NOMI reflects a state of bowel tissue hypoperfusion without mesenteric main vessels occlusion, treatment should seek to reverse the underlying cause. Thus fluid resuscitation, oxygen administration, correction of anemia, optimization of electrolyte balance, antibiotic and low molecular weight heparin (LMWH) represent the first line treatment. Vasoactive agents and other medications causing mesenteric arteriolar vasoconstriction should be avoided or suspended.⁶³ If bowel necrosis is already established, laparoscopy for surgical resection should be considered.^{64,65} Experimental treatments have attempted intra-arterial infusion of vasodilator drugs like papaverine, prostaglandine and iloprost reporting encouraging but still limited results.⁶⁶

Therapeutic Strategies for MVT

In case of non-complicated porto-mesenteric venous thrombosis, first line treatment is simple anticoagulation with LMWH and continued with oral anticoagulant. If bowel transmural damage is clinically suspected (signs of peritonitis) or there are evidences at CTA imaging, then continuous unfractionated heparin infusion should be preferred both for a better monitoring of the anticoagulation level and the chance to be reversed with protamine if surgery is required.⁶⁷

Endovascular treatment which includes mechanical thrombectomy and/or catheter-directed thrombolysis via trans-hepatic or trans-jugular porto-systemic access may be considered. ⁶⁸

DUPLEX ULTRASOUND (DUS) AND ACUTE MESENTERIC ISCHEMIA

Duplex ultrasonography (DUS) has been used in the diagnosis of mesenteric vascular disease. It can reliably detect arterial occlusion/stenosis and venous thrombosis of the main vessels as well as bowel wall thickness and enhancement, abdominal free fluid, hypotonic reflex ileus or *paralyticus ileus*.⁶⁹ Moreover it is widely available, reproducible, relatively inexpensive and without radiation exposure risk. However it is operator dependent and its application can be limited by the presence of bowel gas and respiratory movements.

Nowadays its application is mainly pointed towards the study of chronic mesenteric ischemia and to assess patients after major cardiovascular surgery experiencing abdominal complains. Unfortunately, few are the studies assessing the feasibility and diagnostic accuracy of DUS in acute settings.⁷⁰

MESENTERIC ARTERIES ASSESSMENT

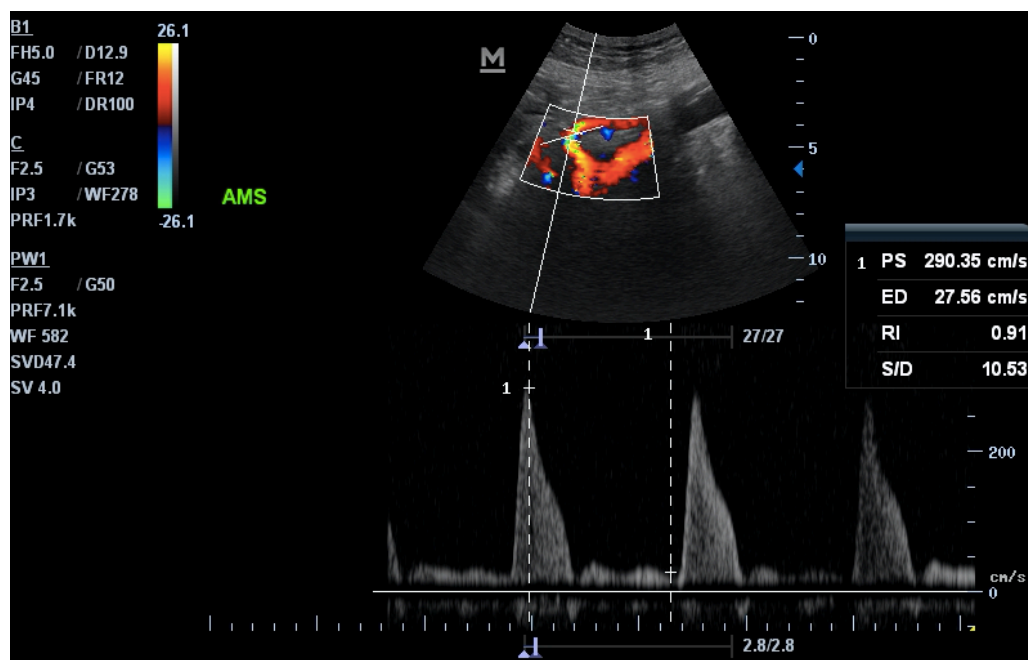
DUS of the mesenteric vessels is usually performed with a 3,5-5 Mhz probe, using grey-scale B-mode, color and doppler analysis using an angle of 60° to assess arterial velocities with a sample volume of 1,5mm. Doppler analysis consists of the evaluation of the “doppler shape” of the trace, the measurement of the peak systolic velocity (PSV) and the end diastolic velocity (EDV). High PSV and EDV correlates with arterial stenosis whilst low values may reflect systemic hypotensive state.⁷¹

The resistive index (RI) calculated with the following formula: $(\text{peak systolic velocity} - \text{end diastolic velocity}) / \text{peak systolic velocity}$, is derived to assess the relationship between PSV and EDV. RI values lower than 0.70 reflect a significant increase of the arteriolar resistance.⁷²

Celiac axis is generally best accomplished in the sagittal plane, whereas its main branches (common hepatic, splenic, and left gastric arteries) are best seen in the transverse view. Its classical ultrasound visualization of the T-shaped bifurcation (seagull sign) on the transverse view is a characteristic landmark. Doppler tracing is usually biphasic with high diastolic velocities reflecting a low resistance circulation to liver and spleen. PSV and EDV normal values are reported to be 80-100cm/sec and 30-65cm/sec respectively.⁷³ PSV >200cm/sec and EDV>55cm/sec correlates with a stenosis >70%.⁷⁴

SMA is best seen in sagittal view of the upper midline abdomen, it arises from the anterior aspect of the aorta then travelling inferiorly 1cm below celiac axis. Doppler tracing is triphasic with higher PSV and lower EDV than celiac axis. PSV and EDV normal values are considered 80-200cm/sec and 20-40 cm/sec respectively.⁷⁵ PSV >400cm/sec and EDV>70cm/sec correlates with a stenosis of >70%.⁷⁶

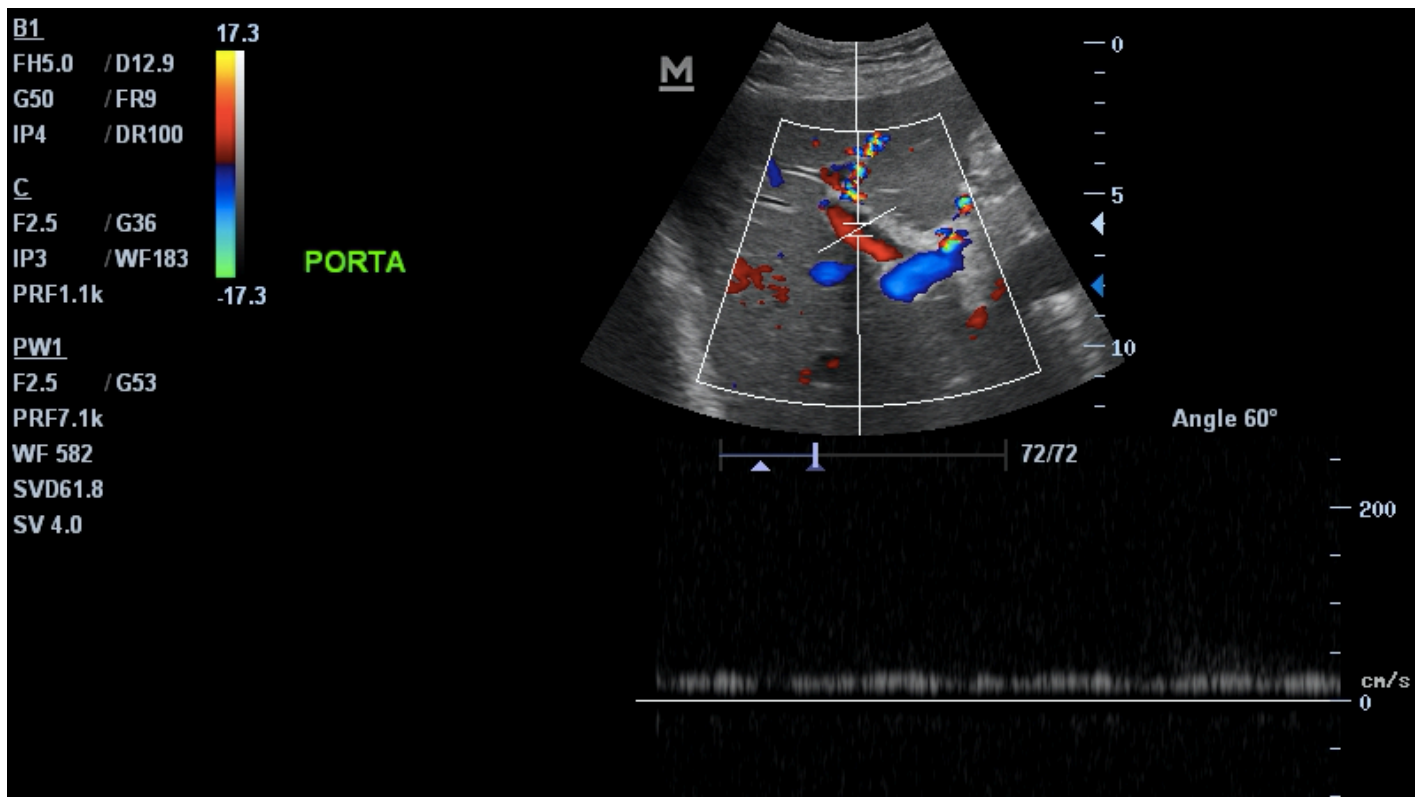
IMA comes off the aorta, just above its bifurcation into the common iliac arteries, in an anterior lateral orientation. As it is thinner than the other mesenteric arteries and usually covered by small bowel, it is really difficult to assess with DUS.⁷⁷



PORTO-MESENTERIC VENOUS ASSESSMENT

Portal vein (PV) and superior mesenteric vein (SMV) occlusion causes impairment in the intestinal vein drainage with consequent vascular engorgement, swelling, and hemorrhage of the bowel wall, with extravasation of fluid from the bowel wall and mesentery into the peritoneal cavity. If not resolved, venous occlusion causes mucosal edema and punctate hemorrhage that progress to widespread hemorrhages. Progression of the thrombosis and inadequate collateral circulation leads to infarction of the jejunum and the ileum.⁷⁸

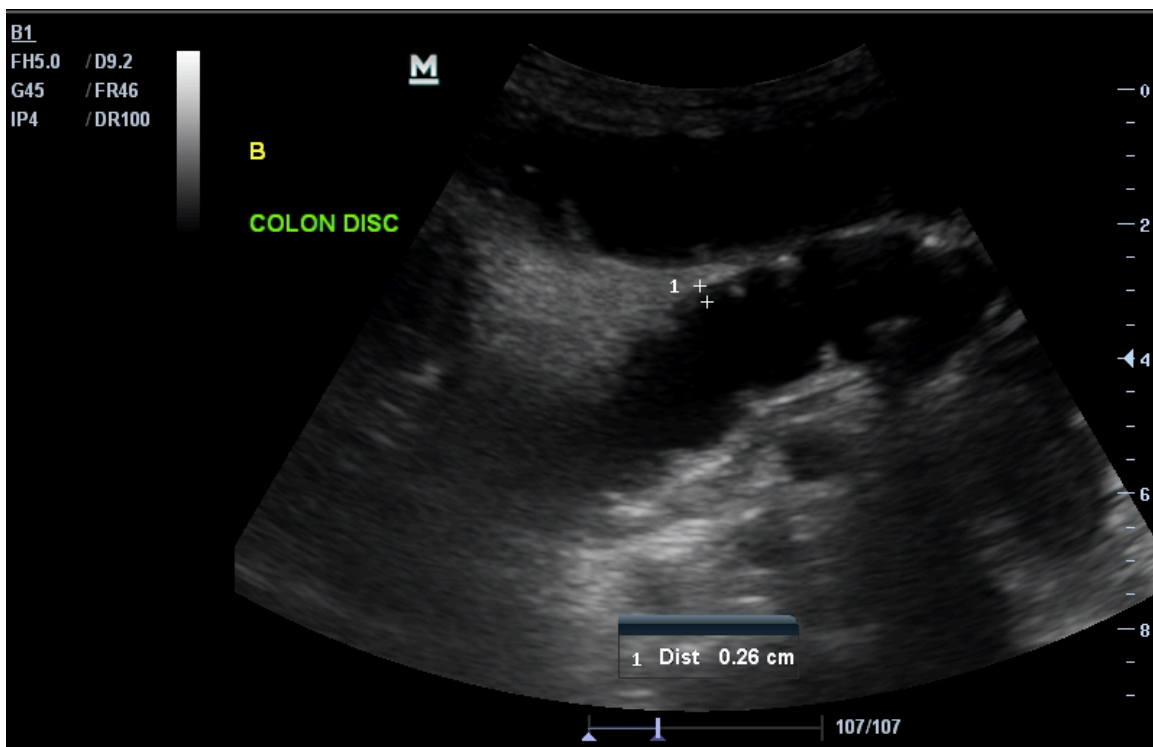
DUS may reveal thrombus at the PV and/or SMV if color-mode is absent and no flow is shown at Doppler tracing.⁷⁹



BOWEL ASSESSMENT

In late phases of AMI, when the ischemic damage is already established causing transmural necrosis, DUS may be useful. Normal bowel wall appearance to ultrasound is made of five layers of alternating concentric hyperechoic and hypoechoic bands with a wall thickness $<4\text{mm}$ and the presence of color/power mode.⁸⁰

Homogeneously hypoechoic intestinal wall as a result of edema and increased intraluminal secretions within the involved segments that occurs earlier in the course of AMI can be detected with DUS. Furthermore decreased peristalsis, mural thickening of the involved segment ($>4\text{mm}$), intraperitoneal gas, and peritoneal fluid can be detected in late phase.⁸¹ However the most specific findings for mesenteric ischemia are intramural gas, portal system gas and reduced color or power mode of the bowel walls.⁸² These findings will be observed in those intestine segments involved by the ischemic insult.



THE RESEARCH PROJECT

AIM OF THE PROJECT

Early diagnosis and treatment are the key points to reduce mortality of AMI.⁸³ Abdomen CTA is considered the radiological test of choice to confirm the diagnosis, however “clinical suspicious” remains the most important feature to drive the diagnostic workup as presenting signs and symptoms are non-specific.⁸⁴ Time-consuming use of inappropriate diagnostic procedures and/or wait-and-see attitude remains the main causes of delayed diagnosis.⁸⁵

Thus a new approach to correctly identify AMI among those patients presenting acute abdominal pain of unknown origin should be sought. In other clinical scenario with similar feature of uncertainty, where an early and specific diagnosis is required to promptly start an appropriate treatment, like for those patients querying pulmonary embolism, clinical diagnostic tools (CDTs) have been created.⁸⁶ To our knowledge, only one diagnostic scoring model has been purposed by Wang et al. for AMI, however it was done on a small population with strict inclusion criteria, based only on laboratory test investigations and not yet verified.⁸⁷ (see Figure 3)

Table 3 Multivariate predictors of AMI and development of the clinical score

Variable	Logistic regression coefficients	Adjusted OR (95% CI)	P value	Point score
WBC				
≤19.6 × 10 ⁹ /L	2.78	16.11	0.04	0.5
>19.6 × 10 ⁹ /L		(1.10, 235.34)		1
RDW				
≤15%	3.32	27.65	0.025	1
>15%		(1.53, 501.02)		2
MPV				
≤9.3 fL	2.78	16.06	0.023	0.5
>9.3 fL		(1.48, 174.50)		1
D-dimer				
≤693 ng/mL	3.76	42.91	0.009	1
>693 ng/mL		(2.56, 718.09)		2

WBC white blood cell, *PLT* platelet, *RDW* red cell distribution width, *MPV* mean platelet volume, *OR* Odds ratio, *CI* confidence interval

Figure 3 The scoring model system suggested by Wang et al. for the diagnosis of acute mesenteric ischemia. A result of >4 would have 97.8% and 91.8% of sensitivity and specificity respectively

Furthermore there are little data about the usefulness of DUS in AMI in acute setting.

Therefore we set out this research project about early identification of AMI in the Emergency Department based on a stepwise approach aiming for the following endpoints:

- PRIMARY END POINT: To create a new clinical diagnostic tool (CDT) for the evaluation of pre-test probability of acute mesenteric ischemia in patients with acute abdominal pain of unknown origin. Furthermore we wanted to validate the Wang et al. novel scoring system for AMI.
- SECONDARY ENDPOINTS:
 - To verify our new created CDR in a prospective population presenting to the Emergency Department with suspected AMI
 - To assess DUS feasibility and diagnostic accuracy to support pre-test probability for AMI

The research project consisted of two different consequential parts: the first was retrospective for the primary end point, the second prospective for the secondary end-points. Each part will be discussed separately.

THE RETROSPECTIVE STUDY

Material and Methods

We retrospectively searched the notes of all patients presented to the Emergency Department of Policlinico San Martino University Hospital, Genoa, Italy and investigated for acute abdominal pain of unknown origin between January 2014 and December 2015.

We used ICD-9 World Health Organization disease classification to identify patients diagnosed with AMI at hospital discharge. Then we matched electronic records related to wards permanence and definitive diagnosis with the respective Emergency Department notes.

Inclusion criteria were as follow:

- Admission for abdominal pain without an obvious diagnosis of origin after first clinical evaluation in the ED;
- They should have undergone abdomen CT angiography, mesenteric angiography, emergency laparotomy or abdomen ultrasound with the specific request to investigate for AMI.

Exclusion criteria were as follow:

- Age<18 years
- Recent abdominal trauma
- Cancer history

- Pregnancy

In order to consider all possible variables related to AMI, we collected information from medical notes about age, gender, medical history, presence of cardiovascular risk factors, comorbidities, vital parameter, laboratory test, radiological imaging test done in the ED, and the adopted treatment.

All patients underwent abdomen CTA, DUS for porto-mesenteric thrombosis, open laparotomy, or angiography. AMI cases were then divided into OMI (signs of emboli or critical stenosis >70% of the arterial mesenteric vessels), NOMI (patency of the main arterial and venous mesenteric branches with signs of reduced or absent bowel wall enhancement, bowel wall thickening, mesenteric fat stranding, pneumatosis suggestive of ischemic insult) and MVT (presence of complete or partial mesenteric veins and/or portal vein thrombosis with or without signs of bowel ischemic insult).

AMI diagnosis within the ED presentation, 3-month mortality, adverse outcome (bowel perforation, septic or haemorrhagic shock, intensive therapy unit admission, cardiac arrest), and length of hospital staying were recorded.

We calculated for each patient the novel scoring model suggested by Wang et al.⁸⁰ giving a 0.5 point for white cell count (WCC) $\leq 19.6 \times 10^9/L$, 1 point for $WCC > 19.6 \times 10^9/L$, 1 point for RDW $\leq 15\%$, 2 points for $RDW > 15\%$, 0.5 point for $MPV \leq 9.3 fL$, 1 point for $MPV > 9.3 fL$, 1 point for $D\text{-dimer} \leq 693 ng/mL$ and 2 points for $D\text{-dimer} > 693 mg/mL$. Its diagnostic accuracy was investigated with ROC analysis.

On the basis of the multivariate regression analysis, we derived an our own scoring model system using all factors significantly associated with AMI, trying to further

adapt it for OMI, NOMI or MVT condition as clinical presentation and management are different.

Furthermore we applied the derived model to our study population in order to verify its diagnostic accuracy.

Statistical analysis

Results were shown as median and interquartile range or percentage. Continuous variables were compared with t-test or Mann-Whitney test when appropriated (for parametric and non-parametric respectively). Categorical variables were compared with Pearson chi-square test. Those variables found to be strongly associated with the outcome measure ($P < 0.05$) were combined using either recursive partitioning or logistic regression. The objective was to find the best combinations of predictor variables, ie, those highly sensitive for detecting the outcome measure while achieving the maximum possible specificity. Building of the regression model proceeded with forward stepwise selection until no variables met the criteria for entry ($P < 0.05$) or removal ($P > 0.10$) for the significance levels of the likelihood-ratio test. The crude and multivariate adjusted odds ratio (OR) with 95% confidence interval (CI) was estimated. The derived CDT was cross-validated by comparing the classification of all patients to their actual status for the primary outcomes allowing estimates, with 95% CIs, the sensitivity and specificity of the score. Then, according to Lee et al., we assigned for β -coefficient < 0.6 , 0.7 to 1.3 , 1.4 to 2.0 , and > 2.1 a value of 1, 2, 3, and 4 respectively.⁸⁸ Finally the receiver operating characteristic (ROC) curve was used to assess diagnostic accuracy of the created rule on the given population. Statistical analysis was performed using the SPSS software version 21 (IBM Corp. © Copyright IBM Corporation et al. Chicago USA).

Results

Between January 2014 and December 2015, 275 were found being investigated for AMI. Of those 56 were not eligible because hospital access was not through Emergency Department, they mainly underwent major cardio-vascular surgery or had long length of stay in ICU. Of the 219 eligible patients, 76 had missing or incomplete medical record so that was impossible to gather all predictive variables leaving 143 patients for full analysis.

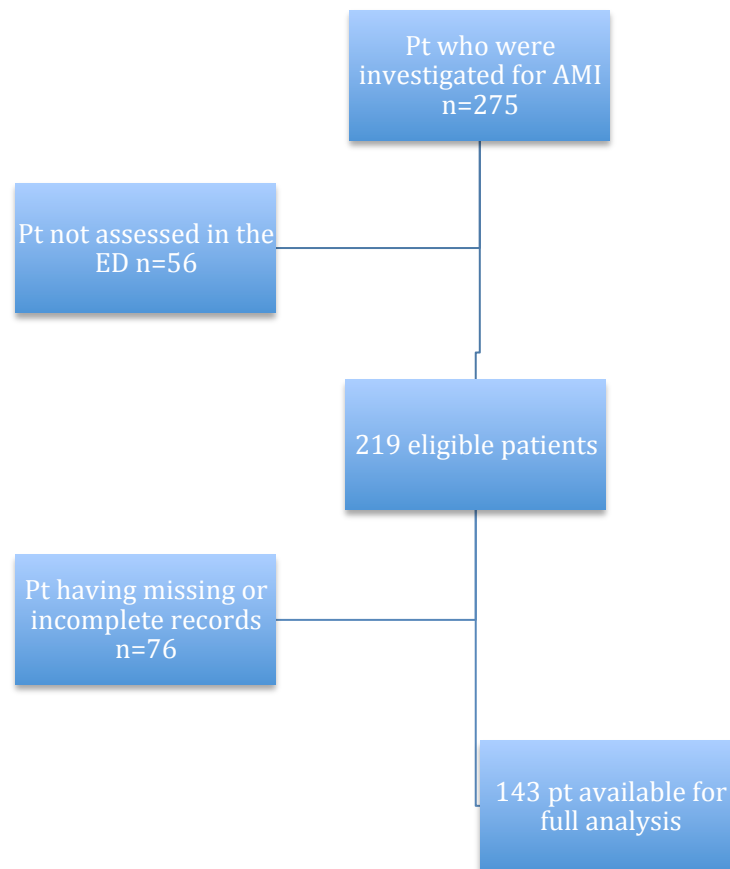


Figure 4. Selection of patients for the study

At hospital discharge, 90 patients had a confirmed diagnosis of AMI, whilst of the 53 non-AMI patients other diagnosis were: diverticulitis (n=17), bowel adhesion (n=9), aortic abdominal aneurism (n=3), acute pancreatitis (n=5), incarcerated hernia (n=4), volvulus (n=5), acute cholangitis (n=3), pneumonia (n=3), no specific diagnosis (n=5). Of the 90/143 patients with AMI, n=15(16%) were classified as OMI, n=29(32%) as NOMI, n=46(51%) as MVT. Table 1 shows the characteristics of the non-AMI and AMI population, AMI population is further divided into OMI, NOMI and MVT.

TABLES 1. Characteristics of patients investigated for AMI

	Non-AMI (n=53)	AMI(n=90)	OMI (n=15)	NOMI(n=29)	MVT(n=46)
Age	73,75±14,5	71,56±14,6	74,27±12,9	81,38±12,7	65,48±13
Female	27(18,9%)	47(32,9%)	9(6,3%)	19(13,3%)	19(13,3%)
Risk Factors					
Smoke	6(4,6%)	14(9,8%)	1(0,7%)	3(2,1%)	10(7%)
High cholesterol	13(9,1%)	24(16,8%)	9(6,3%)	9(6,3%)	6(4,2%)
High blood pressure	26(18,2)	52(36,4%)	11(7,7%)	21(14,1%)	20(14%)
Diabetes	6(4,2%)	13(9,1%)	4(2,8%)	5(3,5%)	4(2,8%)
Family history	4(2,8)	5(5,3%)	3(2,1)	1(0,7%)	1(0,7%)
Comorbidity					
CAD	12(8,4%)	16(11,2%)	5(3,5%)	10(7%)	1(0,7%)
Cerebral vasculopathy	1(0,7%)	15(10,6%)	3(2,1%)	10(7%)	2(1,4%)
Carotid atherosclerosis	0(0%)	5(3,5%)	0	2(1,4%)	3(2,1%)
Peripheral artery disease	3,(2,1%)	9(6,3%)	3(2,1%)	5(3,5%)	1(0,7%)
Atrial fibrillation	4(2,8%)	15(10,5%)	4(2,8%)	8(5,6%)	3,(2,1%)
AAA	1(0,7%)	4(2,8%)	1(0,7%)	2(1,4%)	1(0,7%)
Chronic liver disease	7(4,9%)	32(22,4%)	1(0,7%)	0	31(21,7%)
Medications					
Digoxin	1(0,7%)	4(2,8%)	0	4(2,8%)	0
b-blocker	14(9,8%)	30(21%)	11(7,7%)	13(9,1%)	6(4,2%)
Ca-antagonist	7(4,9%)	8(5,6%)	3(2,1%)	4(2,8%)	1(0,7%)
Signs and symptoms					
Acute abdominal pain(<24h)	34(23,8%)	55(38,5%)	9(6,3%)	17(11,9%)	29(20,3%)
Abdominal pain >48h	2(1,4%)	10(7%)	1(0,7%)	2(1,4%)	7(4,9%)
others	17(11,9%)	14(9,8%)			
Vitals Parameter					
SBP	132,31±28,3	133,8±30	140,71±35,4	139,44±32,3	126,58±24,8
DBP	77,04±13,3	77,3±15,7	79,43±19,1	78,7±18,1	74,8±12,1
Temperature	37,2±0,7	36,9±0,6	37±0,3	36,6±0,7	37,1±0,4
Heart rate	81,6±15,2	99,1±25,3	97,4±31,2	98,3±22,5	89,7±15,3
Laboratory					
Leucocytes	9,94±2,6	11,3±4,9	10,07±3,4	14,5±3,1	9,6±5,6
Neutrophyl	71,6±16,4	78,4±12,9	77±12,5	78,8±9,7	68,1±14
D-dimer	334,5±77,07	405±87	430±14,5	382,7±105,1	490±98
Hospital LOS	20,06±31,2	17,7±32	15,57±18,7	14,3±20,2	20,23±41
Adverse outcome	12(8,5%)	19(13,4%)	4(2,8%)	11(7,7%)	4(2,8%)
Death	14(9,9%)	24(16,9%)	7(4,9%)	14(9,9%)	3(2,1%)

AMI: Acute Mesenteric Ischemia, OMI: Occlusive Mesenteric Ischemia, NOMI: Non Occlusive Mesenteric Ischemia, MVT: Mesenteric Venous Thrombosis, CAD: Coronary Artery Disease, AAA: Abdominal aortic aneurysm, SBP: Systolic Blood Pressure, DBP: Diastolic blood pressure,

Overall AMI mortality was 16,9%, almost doubled with respect to non-AMI group (9,9%). However, in the OMI and NOMI subgroup, mortality reached almost 50% as 7/15 OMI and 14/ NOMI patients died. In the MVT subgroup only 3/46 patients died. Length of hospital stay was 11,5% shorter in AMI population than in non-AMI.

Wang's score was impossible to calculated in 76 patients because our central laboratory stopped to report the MPV value for the emergency department so that it was applied just in 77 cases. ROC analysis for Wang's score diagnostic accuracy for AMI showed an AUC of 0,618 (95% CI 0.45-0.77) with a sensitivity and specificity for the indicated 4 point result of 76,7% and 51,2% respectively.

As we found that OMI and NOMI populations were similar in terms of age, risk factors, comorbidities, medications predisposing AMI we considered these population group together for multivariate analysis.

In Table 2 we reported multivariate regression analysis results of the variables significantly related to AMI ($p < 0.05$), they were:

- the presence of one risk factor
- the cumulative amount of comorbidity
- abdominal pain "out of proportion to clinical signs"
- Systolic blood pressure
- Heart rate
- Neutrophils percentage

Furthermore we found that some variables were related to OMI and NOMI patients but not to MVT.

Factors significantly associated only with OMI and NOMI were:

- Age > 65
- Digoxin, beta-blocker or Ca-antagonist assumption

Factors significantly associated only with MVT were:

- History of chronic liver disease
- Abdominal pain > 48h

Table 2. Factors significantly associated with AMI at multivariate logistic regression

	B	S.E.	Wald	Exp(B)	95% CI per EXP(B)	
					min	max
One RISK FACTOR	0,055	0,24	0,052	1,056	0,661	1,689
Cumulative COMORBODITY	1,191	0,403	8,727	3,29	1,493	7,251
ABdominal pain “out of proportion” to clinical signs with onset <24h	1,27	1,31	0,939	3,581	0,271	47,239
SBP	0,001	0,008	0,006	1,001	0,985	1,017
HR	-0,002	0,015	0,022	0,998	0,969	1,027
Neutrophils_Perc	0,019	0,021	0,856	1,019	0,979	1,062

- Factors significantly associated only with OMI or NOMI at multivariate logistic regression

	B	S.E.	Wald	Exp(B)	95% CI per EXP(B)	
					min	max
Age65	1,118	0,603	3,439	3,059	0,938	9,969
Medications (digoxin or beta-blocker- or Ca-antagonist)	0,36	0,465	0,622	1,30	0,58	3,59

- Factors significantly associated only with MVT at multivariate logistic regression

	B	S.E.	Wald	Exp(B)	95% CI per EXP(B)	
					min	max
COMORBODITY_Chronic liver disease	2,196	1,223	3,225	8,991	0,818	98,818
ABdominal pain >48h	0,99	1,45	0,948	1,19	0,57	5,98

The derived scoring model, so called AMI-score (see Table 3), allowed to assign from 1 to 4 points for each specified item.

As some variables were related to OMI and NOMI but not to MVT and vice versa, we build up the scoring model with six common items and then two specific items for OMI and NOMI together plus two specific items for MVT. These information are quickly achievable in the ED and based on patient general and clinical characteristics, blood test and vital parameters.

Table 3. The derived scoring model for AMI (the so-called AMI-score)

	AMI	To be ADDED querying OMI or NOMI	To be added querying MVT
One CV risk factor	2 point		
Cumulative comorbidity	1 point each		
Abdominal pain out of proportion to clinical signs	4 points		
Altered systolic blood pressure (<90 or >140)	1 point		
Altered heart rate (<60 or >100 bpm)	1 point		
Neutrophils percentage >75	1 point		
Age >65yo		4 points	
Assumption of one of the following medication (Digoxin, beta-blocker or Ca-antagonist)		2 points	
Chronic liver disease			4 points
Abdominal pain onset >48h			3 points

CV risk factors: smoke, hypercholesterolemia, arterial hypertension, diabetes mellitus, family history for cardiovascular disease

Comorbidity considered: coronary artery disease, cerebral vasculopathy, carotid atherosclerosis, peripheral arterial occlusive disease, aortic aneurism, atrial fibrillation,

Afterward we applied each derived score to assess the pre-test probability of OMI-NOMI and MVT. For OMI-NOMI the ROC analysis showed an AUC of 0,733 (CI 95%: 0,62-0,82) obtaining for the best cut-off score >4 91.2% and 47.5% of sensitivity and specificity respectively. For MVT, with a best cut-off score >4 AUC was 0,772 (CI 95%: 0,686-0,859) with 88% and 56% of sensitivity and specificity respectively.

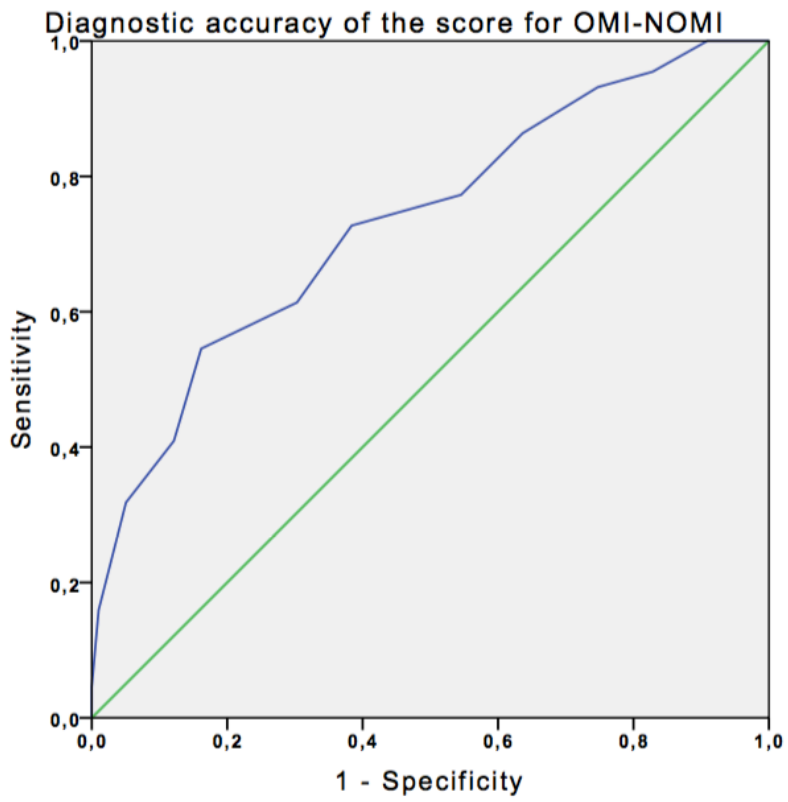


Figure 5. ROC curve of AMI-score for OMI-NOMI

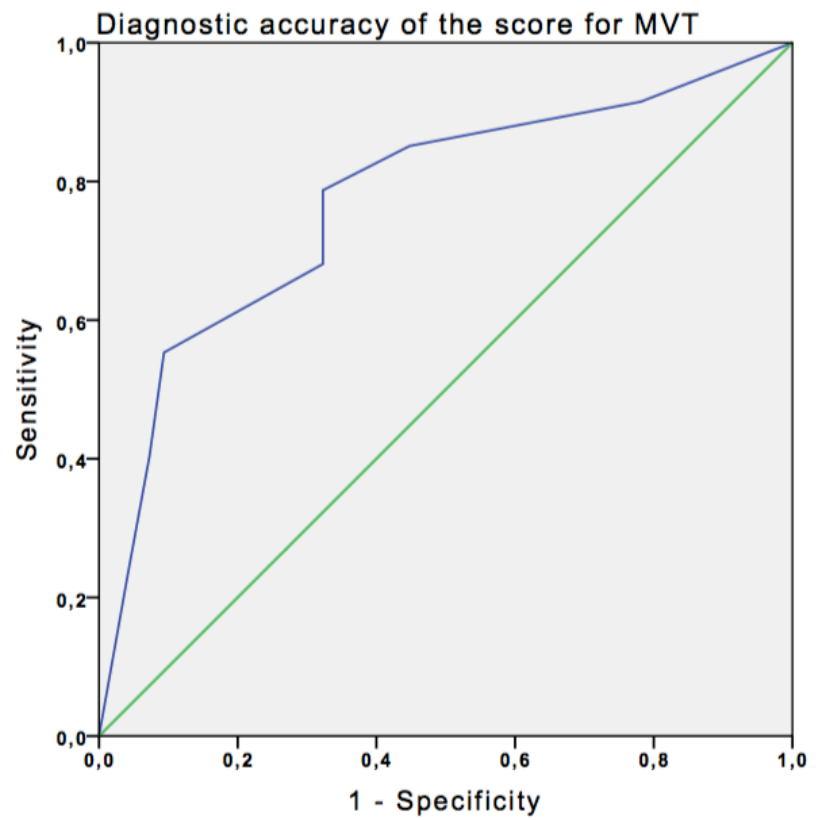


Figure 6. ROC curve of AMI score for MVT

Discussion

We conducted this retrospective observational study to identify a new scoring model to support AMI diagnosis in the emergency department. From multivariate regression analysis we identified six common items for AMI and two more specific items for OMI/NOMI and MVT respectively. We found an acceptable overall diagnostic accuracy (AUC=0.73 for OMI-NOMI and AUC=0.77 for MVT respectively) with high level of sensitivity that may allow to include all patient with possible AMI even if this mean to have a positive score in patients without AMI.

As AMI presentation characteristics are insidious, the score has to represent many aspects of the disease. Patients with at least one cardiovascular risk factors showed an odds ratio of 1,056(CI 95% 0.661-1.68, 2 points assigned by the presence of at least one risk factor). The presence of cardiovascular comorbidities seemed to be strongly related to AMI (odds ratio of 3.58; 95% CI1.49-7.25, 1 point assigned for each comorbidity) reflecting the fact that atherosclerosis is an ubiquitous disease.⁸⁹The item “abdominal pain out of proportion to clinical signs” showed the strongest correlation with AMI (odds ratio 3,58 with 95% CI 0,27-47,23, 4 points assigned). Although it can be argued that this is a subjective judgement and the 95% CI is wide, whether used by experienced physicians may make the difference. Altered SBP, HR and increased neutrophil percentage showed a mild correlation with AMI, but allowed the score to be more sensible for systemic alterations.

About the scoring system suggested by Wang, we were able to calculated it in only 50% of our population because of MPV lacking values. This may have cause calculation bias, however we found a lower diagnostic accuracy than that reported in their work (sensitivity 97.8% and specificity 91.8% for criterion>4).

Furthermore, as MPV is not everywhere a routine test and for example our central laboratory stopped to evaluate it, the score suggested by Wang et al. doesn't seem widely applicable other than reliable.

In our population we found a lower percentage of OMI and higher of MVT than reported in literature ^{5,90}, however this could be partially explained by the fact that the surrounding area of Genoa has an high epidemiological distribution of liver chronic liver disorders. ⁹¹

Looking at the general characteristics of AMI sub-population, we found that MVT seems to have different feature from OMI and NOMI: the population was younger (median age of 65,48 vs 77,8), male gender was prevalent (27/46 vs 16/44) and they had a better outcome in terms of mortality and adverse outcome (see Table 1) in line with Harnik et al. findings.⁹²

Therefore constructing a specific pre-test score for OMI-NOMI and a different one for MVT reflects their different characteristics in terms of clinical presentation and

LIMITATIONS

One of the limitation of this study is a possible selection bias, we had to find patients from a ICD-9 based system with specific key words. In case of incorrect use of the specific code for AMI, many patients may have been overlooked. Furthermore as we had to retrospectively look at the medical notes, many required information were partially or not at all present, therefore we had to remove from analysis even 76 patients. Connected to this, the sample size was heavily outnumbered so that the power of the study was reduced. Nonetheless, considering AMI a rare disease, the sample population given was enough to obtain significant results.

Conclusions

Even if not conclusive and done on a relative small sample, this study may contribute to clinical decision making in assessing patients with abdominal pain of unknown origin in whom AMI has to be considered. As abdomen CT angiography is the best imaging of choice to diagnose AMI, our AMI-score can support the decision to request it earlier during patient workup. The next step of our research project is a prospective validation study of this score with the support of the abdomen DUS.

THE PROSPECTIVE STUDY

Liaison With The Retrospective Study

From the above mentioned retrospective observational study, we identified, on the basis of a multivariate analysis, a diagnostic score to diagnose AMI among patients presenting to the Emergency Department with abdominal pain of unknown origin. The aim of that study was to create a practical clinical diagnostic tool in order to guide physicians toward an early AMI diagnosis.

Successively we projected a prospective study with the main aim to validate this CDT in a real-life population presenting to the Emergency Department with abdominal of unknown origin. Furthermore we decided, as second aim of the study, to boost it with abdomen duplex ultrasound (DUS) to assess whether this early exam may support the diagnosis of AMI.

Material and Methods

This prospective pilot validation study was carried out at the Emergency Department of the Policlinico San Martino University Hospital of Genoa, Italy, between October 2016 and December 2017.

Patients were eligible for the study if they fulfilled all the following criteria:

- age >18 years old;
- complaining symptoms of acute abdominal and/or altered bowel habit and/or hematochezia at ED presentation;
- the clinical need, after initial workup, to request an abdomen computed tomography, possibly with contrast medium for angiography, to obtain a diagnosis;

- evidence of porto-mesenteric thrombosis to abdomen ultrasound
- capacity to sign a written informed consent

Exclusion criteria were any of the following:

- a clear diagnosis after initial medical assessment such as: gallstones, cholecistitis, pancreatitis, acute hepatitis, appendicitis, renal or biliary colic;
- known or found pregnancy and/or pain related to gynaecological known problem
- history of trauma within a month from ED presentation
- suspected alimentary intoxication

Data collection was carried out prospectively and recorded in real time on a standardized clinical research form (CRF). All the following data were reported: age, gender, cardiovascular risk factors, history of cardiovascular disease and liver cirrhosis, vital parameters at ED admission, clinical feature of the abdominal pain, laboratory test (leucocytes, neutrophils, CPK, LDH, D-dimer, venous lactate, C-RP). Length of hospital staying was recorded. Furthermore we reported: adverse outcome during hospital staying described as bowel perforation, hemorrhagic shock, septic shock, cardiac arrest and intensive care unit admission; treatment (surgical, endovascular and/or medical therapy); in-hospital and 3-months mortality.

Then for each patient we calculated the new suggested AMI-score and we assessed its diagnostic accuracy for AMI according to CTA findings. At the previous retrospective study, an AMI-score result >4 in case of suspected OMI-NOMI showed 91.2% and 47.5% of sensitivity and specificity respectively whilst for MVT a result >4 had 88% and 56% of sensitivity and specificity respectively.

MDCT and CT angiography diagnostic criteria

An abdomen MDCT was performed in all patients in the ED as dictated by clinical judgment. The report was used as outcome measure to distinguish between patients with and without acute mesenteric ischemia (AMI).

The timings and decision for MDCT were independent of the study. A plain CT was enhanced with iodinated contrast medium for angiography (including arterial, venous, and portal phase) unless contraindicated. Contrast medium was not infused if there was renal impairment (defined as creatinine > 1.5 mg/dl/ > 150 µmol/l) and/or known allergy to iodine-based contrast media. OMI was diagnosed by the presence of emboli or thrombi visualized as filling defects or critical stenosis respectively in the lumen of celiac axis, superior, or inferior mesenteric artery. NOMI was diagnosed by the finding of patent main arterial and venous vessels with a reduction in enhancement and thickening of the bowel wall. MVT was diagnosed by the presence of intraluminal filling defect and engorgement of the mesenteric veins or the main portal vein with or without signs of bowel wall involvement.

Duplex ultrasound evaluation

All DUS examinations were performed as soon as possible and always within 6 hours from hospital presentation. Time-to-DUS assessment and DUS exam duration were recorded in minutes. Quality of images were classified into four classes: optimal, good, mediocre, and not diagnostic. Every time a patient was eligible for the study, the ED staff contacted the sonographer, an emergency physician who performed all DUS exams. He was trained in basic ultrasound (point-of-care thoracic ultrasound, echocardiography, and abdominal ultrasound) with additional

training in vascular Doppler ultrasound. This was supplemented by further training from a one-day dedicated course on mesenteric vessel ultrasound and a daily experience of abdominal DUS.

The sonographer was blinded to abdominal CTA reports. DUS was performed using a Mindray M7 Premium ultrasound machine using standard abdominal software and a curvilinear phased array transducer (4.5–6MHz). Duplex assessment consisted of the evaluation of the superior mesenteric artery with a beam angle between 40° and 60° and a 1.5 mm gate.⁹³ SMA is the best accessible mesenteric vessel to DUS and we deemed that CA and IMA would have been difficult and unreliable to measure.⁹⁴ Moreover some theories affirm that, as mesenteric circulation is interconnected and an auto-regulation system is promptly activated, even a single vessel altered flow may underline an ischemic insult to gut.^{95,96}

SMA was evaluated in sagittal plane with the duplex gate placed within 2 cm of the aorta. We considered normal peak systolic velocity (PSV) values to be 80–200 cm/s for the SMA.⁹⁷ Thus, PSV abnormal velocities were considered less than 90 cm/s or greater than 190 cm/s for CA and less than 80cm/s or greater than 200cm/s for SMA.⁷¹ High velocities are an indication of stenosis greater than 30%, whereas a reduced or absent flow speed represents subtotal occlusion/occlusion pattern or is expression of low cardiac output or shock state.⁷² We further recorded end diastolic velocity (EDV) (20-40cm/sec values were considered normal) and resistive index (RI) (normal value ≥ 70).^{68,71}

Mesenteric and portal veins were evaluated both with color and duplex mode recording vessels patency, quality of the blood flow, bowel wall features. MVT,

partial or complete, was defined as filling defect of mesenteric or portal veins lumen with absence of color image and no detectable duplex signal.

Bowel wall thickness was sampled for small intestine at the level of right lower quadrant close to the umbilicus or where ultrasound showed obvious abnormality such as: increased wall thickness >4mm, reduced power color enhancement, decreased peristalsis, intramural or intraperitoneal gas, and peritoneal fluid. For colon wall thickness was sampled at the level of left flank (descending colon) or where ultrasound showed the same abnormalities described for small intestine.^{74,75}

Entry to the study did not delay any participants from undergoing diagnostic MDCT imaging because of DUS evaluation.

Ethical review

The study was carried out in accordance with the Declaration of Helsinki and approved by our local ethical committee. Written informed consent was obtained from all patients. The study was registered by the Regional Ethical Committee of Liguria (reference number: 056REG2106).

Statistical analysis

We describe study participants using means, ranges and standard deviations for continuous variables, and frequencies with proportions for categorical variables. To assess the differences between patients with and without AMI, the Student t-test or the Fisher exact test was used to compare quantitative Gaussian or non-Gaussian variables, respectively. The Kolmogorov–Smirnov statistical test was used to verify

the normality of data distribution. Receiver operating characteristic (ROC) analysis was used to assess the diagnostic accuracy of AMI-score>4 for OMI-NOMI and >4 for MVT. DUS variables between AMI and non-AMI population were analyzed and altered values were compared using the χ^2 . Furthermore sensitivity (SE), specificity (SP), positive and negative predictive value (PPV and NPV, respectively), and likelihood ratios of PSV, EDV and RI were calculated against the reference standard of CTA positive for AMI. The Hosmer–Lemeshow goodness-of-fit test was used to evaluate model calibration.

The SPSS software v.21 (IBM Software, Amonk, New York, USA), held by the University of Siena Inc., and Matlab v.5 (The MathWorks, Inc., Natick, USA) package were used for statistical computations and score model design, respectively.

Results

Over a 14-months period, 45 patients were screened for the study but six were excluded as per exclusion criteria and two didn't give their consent leaving 37 patients for full analysis. Follow-up about hospital adverse outcome, treatment and death within three months enrolment was achieved for all 37 patients. 8/37 patients didn't received contrast media at MDCT because of renal failure (six cases) and severe anaphylaxis reaction (two cases).

AMI was diagnosed in eight patients (21,6%), of this two were OMI, six NOMI and two MVT. OMI cases had both SMA involvement, one case for emboli occlusion in a new onset AF and the other was due to critical stenosis from atherosclerosis plaque. Of the six NOMI cases, three had distal ileum, cecum and ascending colon involvement, one the transverse colon and two descending colon and sigma. About

MVT cases just one of the two had signs of bowel ischemia, the other one just superior mesenteric vein and portal vein thrombosis, both of them had cirrhosis.

All other diagnosis are reported in figure 7.

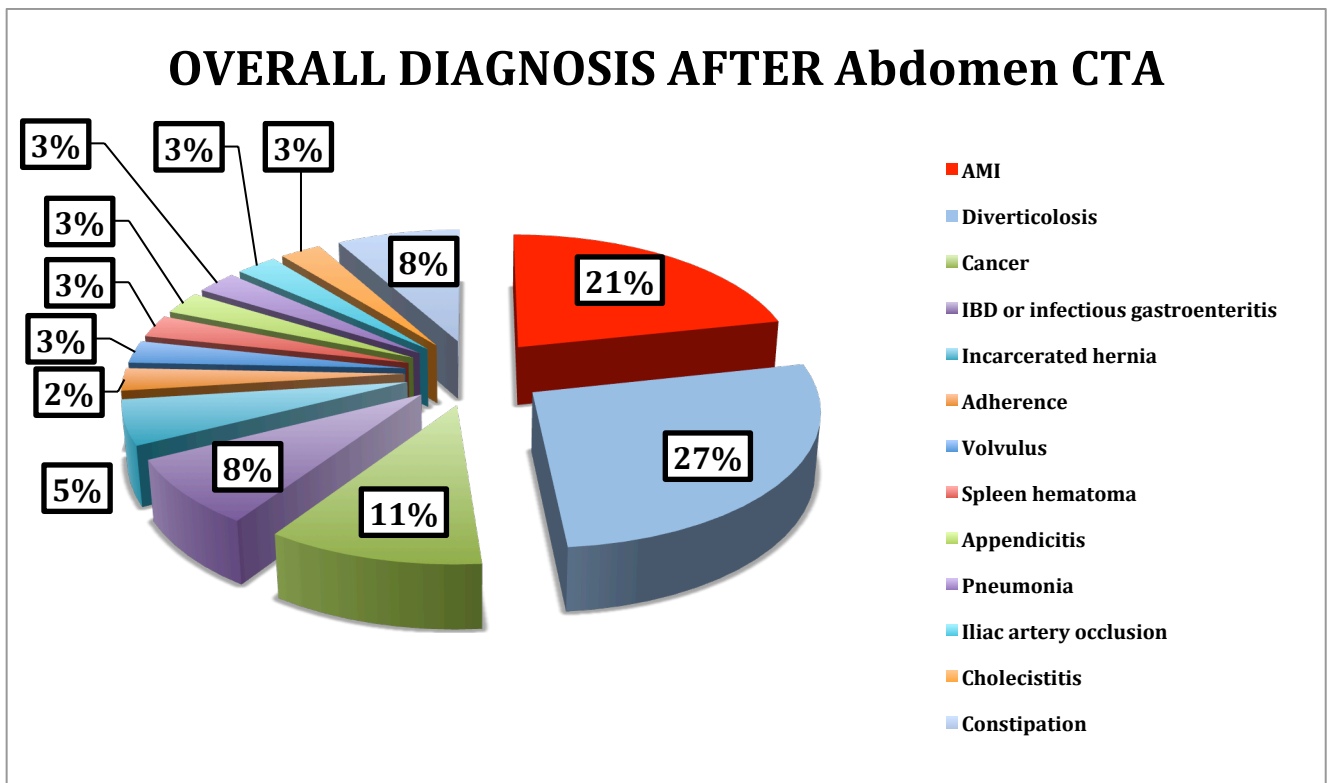


Figure 7 Final diagnosis after ED workup

Patients characteristics of AMI and non-AMI population are reported in Table 4.

Length of hospital stay was $8 \pm 12,6$ SD and $29 \pm 13,31$ SD for AMI and non-AMI group respectively.

TABLES 4. Characteristics of patients investigated for AMI

	Non-AMI n=29	AMI n=8	P value
Age	74±13,94	79,86±15,47	0.33
Female	12 (32,4%)	5(13,5%)	0.28
RISK FACTORS			
Smoke	9(24,3%)	2(5,4%)	0.74
High cholesterol	3(8,1%)	1(2,7%)	0.86
High blood pressure	12(32,4%)	4(10,8%)	0.66
Diabetes	1(2,8%)	1(2,8%)	0.33
Family history	2(5,6%)	0	
COMORBIDITIES			
CAD	5(13,5%)	1(2,8%)	0.74
Cerebral vasculopathy	6(16,2%)	3(8,1%)	0.32
Carotid atherosclerosis	1(2,8%)	0	0.59
Peripheral artery disease	1(2,8%)	0	0.59
Atrial fibrillation	2 (5,4%)	2(5,4%)	0.17
AAA	1(2,8%)	1(2,8%)	0.44
Chronic liver disease	0	2 (5,4%)	0.11
MEDICATIONS	10(27%)	4(10,8%)	0.21
SIGNS AND SYMPTOMS			
Acute abdominal pain(<24h)	19(40,1%)	5(13,5%)	0.07
Abdominal pain >48h	8 (21,9%)	0	0.13
others	12 (32,4%)	1 (2,8%)	0.17
VITAL PARAMETERS			
SBP	141,9±25,4	125,1±23,2	0.09
DBP	82,4±14,9	68,38±8,9	0.016*
Temperature			
Heart rate	82,5±16,8	90,3±23,9	0.29
Oxygen saturation	96,6±2,0	95,8±2,3	0.43
Body temperature	36,9±0,7	37,1±1,3	0.66
LABORATORY TEST			
LDH	252±159	261±44	0.89
CPK	89±83,3	75±15,9	0.43
Leukocytes count	13,24±6,8	9,6±7,2	0,24
Neutrophils percentage	80,2±11,7	75,9±13,7	0.43
Lactate	2,15±1,9	3,65±1,9	0.11
D-dimer	2175±2237	4937±2971	0.12
C-reactive protein	75,3±80,7	35,7±30,3	0.04

AMI: Acute Mesenteric Ischemia; CAD: Coronary Artery Disease; AAA: abdominal aortic aneurysm, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure;

Adverse outcomes were present in 2/8 (25%) of patients with AMI (one hemorrhagic shock and one ICU admission) whereas in 5/29 (17%) of non-AMI group (three suffered bowel perforation, one septic shock and one ICU admission).

Two of AMI patients died within hospital staying (mortality 25%), and two more died within 3-months so that cumulative mortality was 50%. Among non-AMI patients two died within 3-months (6,9%), none during hospital staying.

ROC curve of the AMI-score for OMI-NOMI had an AUC of 0.76(95% CI: 0.52-1) with a sensitivity and specificity of 91% (95% CI: 83,3%-100%) and 35%(95% CI: 27%-46%) respectively for a result>4. ROC curve of the AMI-score for MVT showed AUC of 0.9 (95% CI: 0.76-1.0) with a sensitivity and specificity of 100% and 62% (95% CI 49-71%) respectively. See figure 8 a-b.

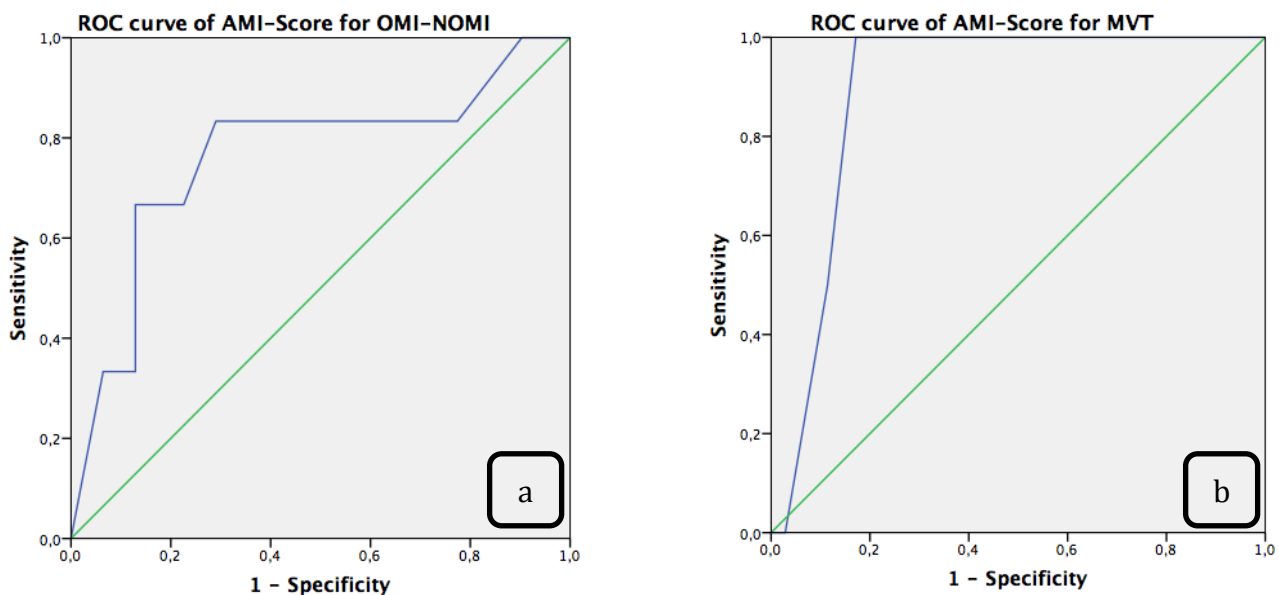


Figure 8. ROC curve of the AMI-score for OMI-NOMI (a) and MVT

DUS of the SMA and bowel was achievable in 35/37 enrolled patients (95%) with an acceptable overall quality of the images (9 were classified as optimal, 19 good, 7 mediocre). The mean execution time was 4,37 min (minimum 2 minutes, maximum 10 minutes).

About SMA evaluation, PSV had mean velocity of $279,17 \pm 186,1$ SD cm/sec in AMI group whereas $188,7 \pm 105,66$ SD cm/sec in non-AMI group ($p=0.14$). SMA EDV mean velocity was $44 \pm 24,8$ SD cm/sec and $40,4 \pm 27,4$ cm/sec in AMI and non-AMI group respectively ($p=0.73$). RI mean was $0,78 \pm 0,12$ and $0,79 \pm 0,07$ in AMI and non-AMI group respectively ($p=0.83$). (see figure 9-10-11)

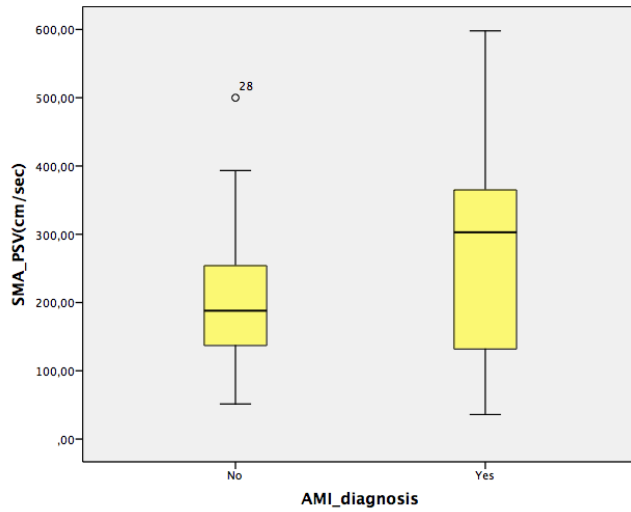


Figure 9. Comparison of SMA PSV velocities between AMI and non-AMI group

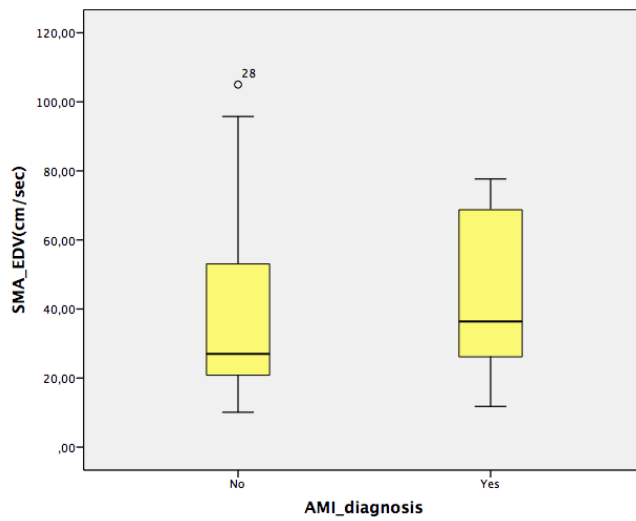


Figure 10. Comparison of SMA EDV velocities between AMI and non-AMI group

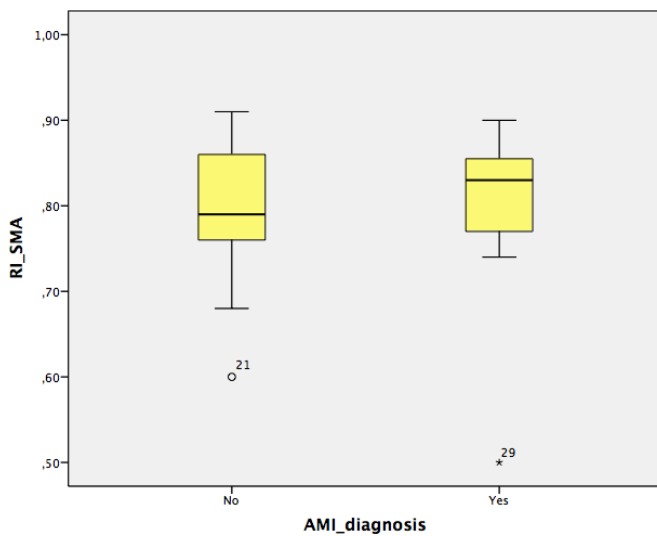


Figure 11. Comparison of SMA RI ratio between AMI and non-AMI group

MVT was detected in both cases, one with isolated complete portal vein thrombosis and the other one with portal and superior mesenteric vein filling defect due to thrombosis then confirmed by abdomen CTA.

Bowel wall alterations were found in 5/8 (63%) patients with AMI (four related to small intestine and one at the level of descending colon) and in 11/27 (41%) without AMI.

Altered SMA PSV (value <80 or >200cm/sec) were present in all of the eight AMI patients and in 15/27(55,6%) without AMI showing a sensitivity, specificity, positive and negative predictive value of 100%, 44,44%, 34,78% and 100% respectively(p=0.02). SMA altered EDV and IR didn't show a significant correlation with AMI (p= 0.82 and 0.86 respectively).

AMI-score diagnostic accuracy boosted with SMA PSV altered value, to which 3 points were assigned as ODDs ratio was 1.53 (95% CI 1.13-2.06), are reported in Table 5 and ROC curve in figure 12.

Table 5. AMI-score and AMI-score plus DUS diagnostic accuracy for AMI

AMI-score validation					
	AUC	95% CI	Sensitivity	Specificity	P value
For OMI-NOMI	0.76	0.83-1	91%	35%	0.015
For MVT	0.90	0.80-1	100%	62%	0.039
AMI-score+DUS alteration					
	AUC	95% CI	Sensitivity	Specificity	P value
For OMI-NOMI	0.81	0.59-1	100%	49%	0.017
For MVT	0.92	0.80-1	100%	51%	0.047

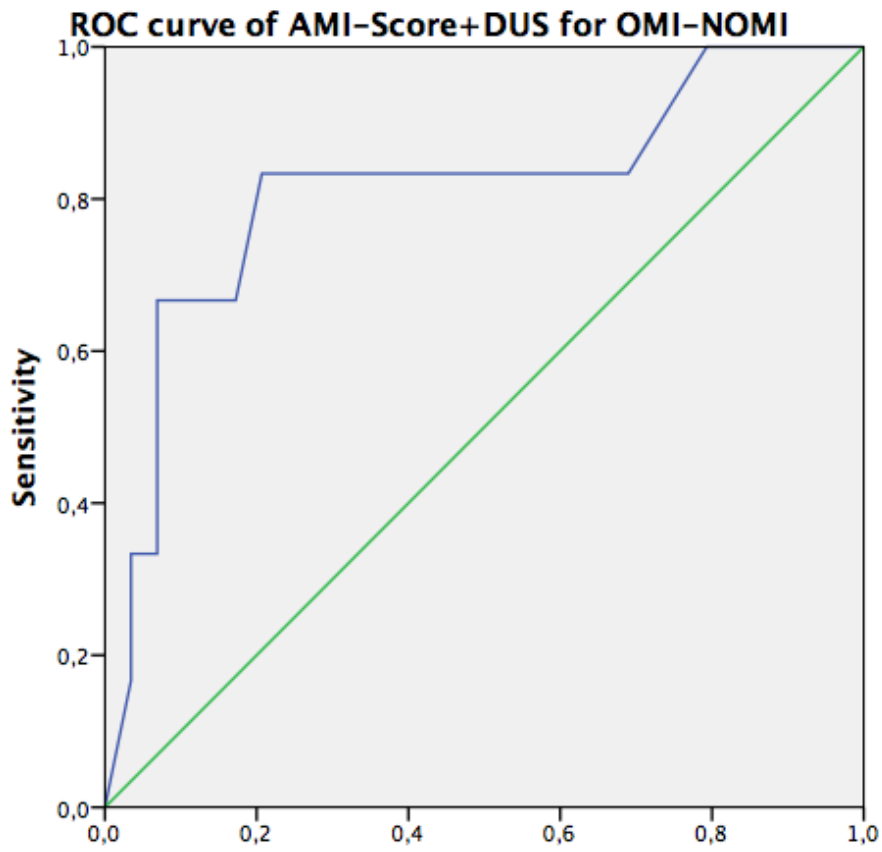


Figure 12. ROC curve of AMI-score boosted with altered SMA PSV at DUS

Discussion

With this prospective validation study we tried to verify the usefulness of a novel diagnostic scoring system to assess patients presenting to the Emergency Department for abdominal pain of unknown origin suspected of having acute mesenteric ischemia.

From the previous retrospective study we created the AMI-score consisting of six items plus two items for each OMI-NOMI or MVT query. The score was based on a multivariate regression analysis of patients investigated for AMI. From that analysis, the AMI-score result >4 was found to have for OMI-NOMI 91.2% and 47.5% of sensitivity and specificity respectively and for MVT 88% and 56% of sensitivity and specificity respectively.

In this pilot validation study, AMI-score confirmed a good overall accuracy for OMI-NIMO (AUC was 0.73 and 0.76 in the retrospective and prospective study respectively) and performed even better for MVT (AUC was 0.77 and 0.90 in the retrospective and prospective study respectively).

Wang et al. proposed a novel scoring system for AMI based just on laboratory tests (RDW, WBC, MPV and D-dimer) with optimal diagnostic accuracy (sensitivity 97.8%, specificity 91.8%, PPV 89.8, NPV 98.2, LR+ 11.93, LR-0.2).⁸⁰ In our study, it was impossible to apply that score as, during the investigation period, our laboratory was not allowed to measure MPV values in emergency for a specific spending review policy. Moreover in that study they excluded patients with chronic liver diseases, chronic renal diseases, hematological diseases and who was receiving immunosuppressive therapy because of altered blood count test. That population seems too selected when compared to the general population presenting to the

Emergency Department, therefore that score is weighted by poor generalizability.⁹⁸ AMI was found in 8/37 (21%) of our population, an higher rate than that reported in literature attested around 1/1000 admission for abdominal pain.^{3,5} However our population study was demanding as per inclusion criteria because obvious causes of abdominal pain didn't entered the study. Moreover the overall presence of AMI may be underestimated as many studies found it more frequently that expected if sought properly.²⁹ Rozycki et al. found 53/300 (18%) AMI among people undergone emergency laparotomy for acute abdomen of unknown origin and Kärkkäinen et al. found that AMI is more common in patients with age>75yo than acute appendicitis or rupture of abdominal aortic aneurism.^{2,99}

Regarding AMI aetiology, we found an higher rate of NOMI than OMI (50% vs 25%) differently from what is reported in literature.^{1,5} In our series 8/37 patients didn't received contrast media and two of them were diagnosed with NOMI. In these patients the main vessels were not evaluated so that a proper diagnosis of OMI was difficult to make. In recent years, new radiological MDCT techniques are improving their capacity to assess the mesenteric vessels even without contrast media, unfortunately we don't have this possibility in our center.¹⁰⁰

Adverse outcomes and mortality rate at 3-months were more common in AMI than non-AMI population (25% vs 17% and 50%vs6,9% respectively) confirming a poor prognosis for the ischemic disease.^{8,101} In our series none of the OMI patients underwent endovascular treatment because of the decision of the interventionist radiology. This trend seems to confirm that, despite the increasing utilization of new reperfusion treatment such endovascular thrombectomy and stent application, mortality remains high.^{9,102} Although new diagnostic and treatment technology are

available, early diagnosis and reperfusion strategies are the milestones to reach for better prognosis.^{50,53}

Diagnostic DUS was achievable in 95% of our series confirming that SMA is accessible to ultrasound.¹⁰³ Even though most of the studies about DUS of the mesenteric vessels are made in non-acute setting, it showed good feasibility and reproducibility.^{66,68} DUS seems also feasible in a ED context as mean execution time was less than five minutes. The main restriction was related to the presence of experienced sonographer being able to perform it.

Even if not statistically significant, the mean of SMA PSV was higher in the AMI group than non-AMI (279,1cm/sec vs 188,7 cm/sec), suggesting the presence of arterial stenosis. Moneta et al. suggested a cut-off of 275 cm/sec or greater or no flow to as indicator of SMA stenosis >70% and this was confirmed in our population.¹⁰⁴ Furthermore SMA EDV mean velocities of 44 cm/sec in AMI group correlates, according with Abu Rahma et al. findings, with a stenosis of 50%. However a proper comparison with those studies cannot be made as they used prepared and fasting patients for ultrasound whilst in our series it wasn't possible to wait for a preparation. RI values were similar in both AMI and non-AMI population. This may suggest a little role of RI alteration in AMI diagnosis. Ripolles et al. found similar RI values higher than 0.60 in both patients with and without ischemic colitis .¹⁰⁵

MVT was detected in both of two cases presented giving a very good sensitivity and even specificity. Both of them had chronic liver disease so that clinical suspicion was high. Portal vein showed a very good accessibility to DUS and it's role is relevant.¹⁰⁶ As superior mesenteric vein is more difficult to assess than portal vein,

Bradbury et al. suggested the use of US compatible intravascular contrast agents that were not considered in this study.¹⁰⁷

Bowel alterations were present at DUS in 63% of AMI compared to 41% non-AMI group. However these findings have more likely a prognostic meaning other than a diagnostic one.¹⁰⁸ As we reported earlier, the most specific bowel alterations of DUS for AMI are intramural gas, portal system gas and reduced color or power mode of the bowel walls but are not easy to detect.⁷⁶ Thus duplex evaluation of the mesenteric vessels can be considered a better way than bowel wall evaluation to investigate patients querying AMI.¹⁰⁹

Altered SMA PSV value confirmed to be strongly related to AMI as expressed by the high sensitivity and NPV of 100%, remarkably none of AMI patient had a normal SMA PSV. This finding seems to confirm previous data from a pilot study reported by Sartini et al. who investigated DUS alteration of CA and SMA in patients with known cardiovascular disease.⁶⁶ Differently from that study, in our series SMA PSV was more sensitive (100% vs 66%) and less specific (44,4% versus 63%) for NOMI. It is difficult to find an exhaustive explanation for these differences, nonetheless we could argue that our population was less selective as they included just patients with known cardiovascular disease. Therefore in a more homogenous population could be more difficult to find significant differences other than in a undifferentiated population like ours. This was the only study we could find about SMA evaluation with DUS in acute setting.

LIMITATIONS

This study has many limitations. First of all, sample size was not wide enough to give a sufficient power for generalization. To obtain a power of the study of 80%, we

estimated a sample size of at least 150 patients that we weren't able to achieve during study period. A possible explanation of having recruited less than expected, is linked to the availability of the sonographer. As he was the only one in charge for DUS, if we would have not been able to perform DUS within 6 hours from admission, a potentially eligible patient would have not been enrolled in the study. The restriction of having just one sonographer didn't allow us to perform an inter-observer analysis about DUS evaluation. Finally bowel evaluation with DUS was not systematic and celiac axis and inferior mesenteric artery were not evaluated with DUS, that data could have contribute to a more complete assessment of DUS.

Conclusions

AMI is a time-dependent life-threatening condition in which early diagnosis and treatment are mandatory to reduce mortality. High clinical suspicion is often the only way to suspect AMI among patients presenting with acute abdominal pain of unknown origin. Abdominal CT angiography is the imaging of choice, however other pre-test tool to support the physician in this difficult diagnosis have not been yet identified. This prospective study validates a new clinical diagnostic tool, the so called AMI-score, to support physicians in the diagnosis of AMI with good overall accuracy. Furthermore SMA PSV alone at DUS can increase the sensitivity for AMI and a normal value can rule it out. Unfortunately the sample size was limited so that further, wider studies are needed to both confirm the usefulness of the AMI-score and of DUS.

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