The Feasibility of a Radiological Score Based on Quantified Analysis of Computed Tomography Signs for Recognizing Salvageable Bowel in Acute Mesenteric Ischemia: A Retrospective Analysis of Prospective Study

Primary study investigator: Martin Reim MD, PhD. Department of Radiology, Tartu University Hospital, Estonia

Steering committee: Joel Starkopf, Annika Reintam Blaser, Kadri Tamme, Karri Kase, Marko Murruste, Merli Mändul

Synopsis

Computed tomography (CT) is the standard modality for scanning patients with critical acute abdominal conditions, including suspected acute mesenteric ischemia (AMI). CT imaging can potentially differentiate between reversible and irreversible ischaemic damage of the bowel. This moment is pivotal in selecting the treatment strategy for AMI – in the absence of irreversible damage; reperfusion therapy can preserve intestinal viability, thereby avoiding the need for bowel resection. The present study tests the hypothesis that combining several symptoms may enhance the diagnostic performance of CT scanning in detecting salvageable bowel in patients with AMI. This study is an ancillary component of the AMESI study (Clinical Trials: NCT05218863) – a prospective, multicentre observational study aimed at identifying the incidence and describing the outcomes of acute mesenteric ischemia (AMI) in adult hospitalized patients. The ultimate purpose of the present study is to create a computed tomography-based radiological score for the assessment of bowel viability in patients with AMI.

Background

Computed tomography (CT) is the standard modality for scanning patients with critical acute abdominal conditions, including suspected acute mesenteric ischaemia (AMI)(1). AMI is a disease with high lethality that is often difficult to diagnose due to non-specific symptoms and the absence of diagnostic biomarkers, and it lacks a standardized therapeutic concept. There are different types of AMI that can be differentiated by aetiology: arterial occlusion, venous occlusion and non-occlusive form of AMI. Non-occlusive mesenteric ischaemia (NOMI) occurs in patients with debilitating comorbid conditions such as shock, haemorrhage, surgery, dialysis, hypovolemia, cardiac disorders, pancreatitis, vasoactive treatments, intoxications, or intense exercise [2].

CT with contrast media enhancement has become the most accurate technique for diagnosing AMI, with a reported specificity between 90 and 100% [3,4], and is considered the first-line imaging modality when AMI is suspected. In addition to recognition of AMI, CT imaging has the potential to differentiate between reversible and irreversible ischaemic intestinal damage [5, 6]. **This is a pivotal moment in choosing the treatment strategy –** in the absence of irreversible damage; reperfusion therapy can restore intestinal viability and thus avoid bowel resection.

Various radiological signs are routinely used to detect bowel ischaemia in CT imaging. The list includes vascular – occlusion of mesenteric arteries or veins – and bowel signs – bowel dilatation, decreased or absent bowel wall enhancement, pneumatosis intestinalis, gas in the mesenteric or portal veins, and bowel wall thinning (Table 1). The capability of these signs to describe the stage of ischaemia has been addressed in some studies. A recent meta-analysis demonstrated that bowel wall thinning, decreased or absent bowel wall enhancement, bowel dilation, pneumatosis intestinalis, porto-mesenteric venous gas, and mesenteric artery occlusion are independent risk factors predicting transmural necrosis (5), whereas decreased or absent bowel wall enhancement and bowel dilation were predictive for

transmural necrosis also in venous occlusive AMI. The same meta-analysis showed that bowel wall thickening and increased bowel wall enhancement were not predictive of transmural necrosis (5). Importantly, while the specificity of these radiological findings, when considered individually, is considerably high—up to 98%—the sensitivity remains very low, ranging from 30% to 40% (5).

Based on this, we hypothesize that **combining multiple signs may enhance the diagnostic performance of CT scanning in distinguishing various stages of ischemic bowel damage.**

From a practical perspective, it is important to predict who **requires bowel resection** and who has **potentially salvageable bowel**. Bowel resection is a disabling surgery that significantly affects a patient's quality of life. Whenever possible, it should be avoided. If the bowel is salvageable, an endovascular procedure can restore mesenteric blood supply – this allows avoiding laparotomy and is considerably less traumatic for the patient.

The present study will elucidate whether the presence of five common radiological bowel signs on CT, either alone or in combination, may distinguish between no bowel ischaemia (suspected AMI) vs. reversible (AMI treated without bowel resection) vs. irreversible ischaemic damage (AMI treated with bowel resection).

To accomplish this, CT scans from patients enrolled in the multicentre international study (The AMESI study, Clinical Trials: NCT05218863) will be collected and subjected to retrospective analysis by the investigating radiologists. After analysing predefined radiological signs separately for their association with the need for bowel resection, the feasibility of combining different CT findings will be explored with the goal of **establishing a practical CT-based radiological scoring system for separating patients with reversible and irreversible bowel ischaemic damage**.

As different subtypes (arterial, venous, and non-occlusive mesenteric ischemia) have different pathoanatomical courses, differences in radiological bowel signs may be expected. To overcome this variability, we will first elaborate the score based on all patients with a confirmed diagnosis of AMI. As a second stage, we will test the score by including only patients with arterial occlusive AMI. If these two created scores appear to be different, we will test them mutually and in subgroups of other subtypes of AMI. The ultimate goal is to have one radiological score identifying the magnitude of bowel damage that could be used for any form of AMI, with possible minimized adaptations needed subtypes.

Considering the low number of venous AMI and NOMI we will primarily not create separate scores for these subtypes. If the performance of created scores appears insufficient in our study, these subtypes need to be assessed in a separate study.

Objectives

The primary objective of the study is to **create a CT-based AMI score using radiological signs that would enable the differentiation between patients with salvageable and non-salvageable ischemic bowel damage**.

The specific objectives are as follows:

- To describe the prevalence of common radiological bowel signs (Table) in AMI patients with and without irreversible ischaemic damage of the bowel.
- To assess the prognostic capability of these radiological bowel signs, both individually and in combination, for predicting irreversible ischaemic damage of the bowel.

- To describe the prevalence of common radiological bowel signs in patients with confirmed AMI vs. suspected but eventually non-confirmed diagnosis of AMI
- To describe the prevalence of common radiological bowel signs in patients with different subtypes of AMI (arterial occlusive, venous, NOMI, other/unclear).

Study questions

1) What is the frequency rate of common radiological bowel signs (Table 1) among AMI patients with and without salvageable bowel?
2) Is it possible to distinguish the AMI patients with and without salvageable bowel with the use of a CT-based AMI score composed of common radiological signs?
3) Is it possible to differentiate the patients with and without AMI with the use of CT-based AMI score composed from common radiological signs?

Hypothesis

It is possible to differentiate between AMI patients with salvageable and non-salvageable ischemic bowel damage using the score based on CT radiological bowel signs.

Study outcomes

Primary study outcomes: Frequency rate of common radiological signs in AMI patients with and without salvageable bowel. Radiological score value in AMI patients according to the stage of bowel ischaemic damage.

Secondary study outcomes:

Frequency rate of common radiological signs/findings among patients with confirmed and suspected but eventually not confirmed AMI.

Performance of the radiological score in patients with different types of AMI.

Methods

This is a substudy of the AMESI study - "Incidence, Diagnosis, Management, and Outcome of Acute Mesenteric Ischaemia: A Prospective, Multicentre Observational Study." As of the end of August 2023, a total of 705 patients from 32 study sites worldwide have been enrolled, with 418 of them having confirmed cases of AMI. For patients with confirmed AMI, comprehensive data collection concerning diagnostics, management, and long-term outcomes has been completed (refer to Appendix 1).

Patients:

From the final AMESI cohort, we will select 6-7 sites limited to Europe due to logistical reasons related to the installation of software for the transmission of full CT investigations in impersonalized form. We expect to obtain images of at least 100 patients with confirmed AMI. Only study sites with more than 20 patients in total enrolled in the study will be asked to contribute radiological data. The CT scans will be gathered through AMESI's dedicated international online platform, and a retrospective visual and

quantitative analysis of pre-defined radiological CT signs and bowel perfusion will be conducted by two independent investigators (blinded to clinical outcome) in Tartu, Estonia.

The control group consists of 100 patients with suspected but not confirmed AMI. First, from AMESI study the CT scans of patients with suspected but not confirmed AMI will be collected through the same centres and platform as described above.

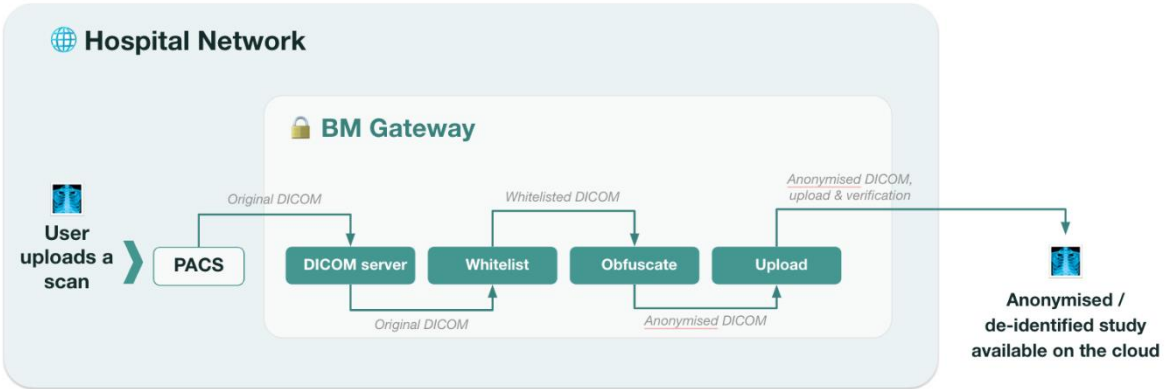
Ethics:

Ethical approval for the study will be obtained from the Ethics Committee, University of Tartu, Estonia as an amendment of the ethics approval for the AMESI study.

The evaluation of radiological data will be performed retrospectively and therefore will not have an impact on the clinical decision-making in the treatment of the selected patients. All measures to protect personal health information will be taken and the requirements set by the EU directives (GDPR) and local authorities will be met.

A special dedicated study server will be set up/used to transfer data from included centres to the AMESI database using a locally installed Gateway. In the local Gateway, it is ensured that the patient's medical image is being transferred into the Tartu University/AMESI cloud - no personal data can be explicitly or implicitly derived from that cloud, to ensure confidentiality. Only pseudonymised CT scans with all personal data removed will be transferred. Patients are identified through their patient ID (pseudonym) in the AMESI study. For this, a secure and robust Gateway to de-identify medical images in a hospital network before sending the images to the cloud will be installed in participating hospitals.

The data inside the included CTs can be divided into three categories - explicit personal data (e.g. patient's name, address), implicit personal data (e.g. patient ID, CT scan ID), and non-personal data (e.g. CT-specific data like image orientation). To achieve de-identified processing of data, Gateway is installed in a hospital's network that performs pseudonymization of medical images, before they are sent to the cloud. The first step in pseudonymization inside Gateway is to remove all explicit personal data (e.g. patient's name, address) - we do not process this data. Then Gateway obfuscates implicit personal data (e.g. patient ID, CT scan ID). The goal of obfuscation of IDs is to avoid getting original IDs when the data is sent to the UT/AMESI cloud. The obfuscated token will be mapped with the original AMESI study patient ID in the Gateway and will reside securely only inside the hospital's network.



With the use of locally implemented virtual PACS node/Gateway, automated pseudonymization steps are carried out to collect radiological imaging data to the UT/AMESI study dedicated server, physically located in Tartu University server park.

The imaging data is stored as DICOM files in a buckets and folders structure. Both the database and the file storage are encrypted at rest. After the completion of the clinical investigation, the data for the analysis will be exported to a static format (comma-separated values, CSV) and provided to the Study Data Manager. Other people will not have access to the exported data.

Ensuring Data Integrity:

Processes to guarantee data integrity are in place to maintain it:

1. Double-checking CT Volume: An integral part of ensuring data integrity is validating the consistency between acquired CT volume data and the original data housed in the hospital. We rigorously double-check the number of slices in the acquired CT volume against its original counterpart to ensure no data loss or discrepancies.
2. DICOM Tag Verification: To ensure comprehensive and intact data, we scrutinise the acquired data to confirm the presence of all required DICOM tags and their corresponding pixel image data.

The AMESI database of pseudonymized CT-s can be accessed via an online platform with the personal identification of selected and authorized study group members. For participants in the AMESI study, the consent to use the clinical and imaging data has been obtained or waived at enrolment, based on local ethics rules. A centralized collection of radiological images was planned in the study protocol of the AMESI study. Installation of software for pseudonymizing CT images will require additional institutional approval from each site.

Data collection:

Patients' clinical and demographic characteristics, including baseline data, AMI event data, management data, histology data, and hospital outcome data will be retrieved from the RedCap database of the AMESI study (Appendix 2), or from the Tartu University Hospital patient data management system.

Data Retention:

The data collected during the study will be stored securely on Tartu University servers till 31.12.2039 and will be securely removed after this date. Only authorised study team members will have access to the data.

Allocation of patients into study groups:

To test the hypothesis, the study patients will be divided into the following study groups:

	Control Cases	Patients with confirmed AMI. Target: 100 - 200	
		AMI patients with salvageable bowel	AMI patients with non-salvageable bowel
No of pt	Target: 50-100	Target: 50-100	Target: 50-100

Definition of the patient group	Patients included in the AMESI study as suspected AMI .	**Patients included in the AMESI study with confirmed AMI, who did not undergo bowel resection** Patients with one of the following: 1) treated endovascularly and did not undergo bowel resection secondarily 2) received surgical revascularization without bowel resection (initial or secondary) 3) received explorative laparoscopy or laparotomy without the need for bowel resection (initially or secondarily) 4) received conservative treatment without the need for secondary bowel resection	**Patients included in the AMESI study with confirmed AMI who (one of the following):** 1) underwent bowel resection initially 2) underwent bowel resection secondarily 3) did not undergo bowel resection because non-salvageable bowel 4) were changed to palliation due to the progression of ischaemia after any initial treatment with curative intention (including endovascular and conservative)

Radiological Methods:

CT scans with intravenous contrast media relevant to the hospitalization of selected patients from the AMESI study cohort will be pseudonymized and uploaded to the online AMESI database. The selection of CT scans will be based on the initial diagnostic hypothesis of acute abdomen or suspicion of AMI.

Inclusion Criteria: CT scan of the entire abdominal cavity / full body using intravenous contrast media.

Exclusion criteria: Scans without the use of an intravenous contrast media or those covering only a partial area of the abdomen will be excluded.

Two radiologists, who will be blinded to the original radiology report, clinical diagnosis and outcome of the patient, will review the CT scans. The CT images will be screened for radiological signs indicative of mesenteric ischaemia (Table 1). The presence of these signs will be recorded as indicated in the Table. In order to develop a radiological score, the bowel signs are used.

Statistics

Obtaining radiological data:

Interobserver agreement for CT findings will be determined with the κ statistic and classified as follows: κ = 0–0.2, slight agreement; κ = 0.21–0.4, fair agreement; κ = 0.41–0.6, moderate agreement; κ = 0.61–0.8, substantial agreement; and κ = 0.81–1, almost perfect agreement.

Disagreements between the two reviewers will be resolved by consensus. Consensual data will then be used for final statistics.

Descriptive statistics:

We will compare epidemiological data and CT signs between patients with and without salvageable bowel damage. Pearson Chi-square or Fisher tests will be used for the comparison of categorical variables, and the Student t-test or Wilcoxon rank-sum test for the comparison of continuous variables as appropriate. A frequency table for the occurrence of radiological symptoms in study groups will be constructed.

Workout of radiological CT-score

In order to develop a radiological score, the bowel signs are used (Table 1, 3-7). We will compare CT signs

1) between the patients with salvageable and non-salvageable bowel damage;
2) between the patients with confirmed and suspected but eventually not confirmed AMI. The conceptual approach is presented in Figure 1.

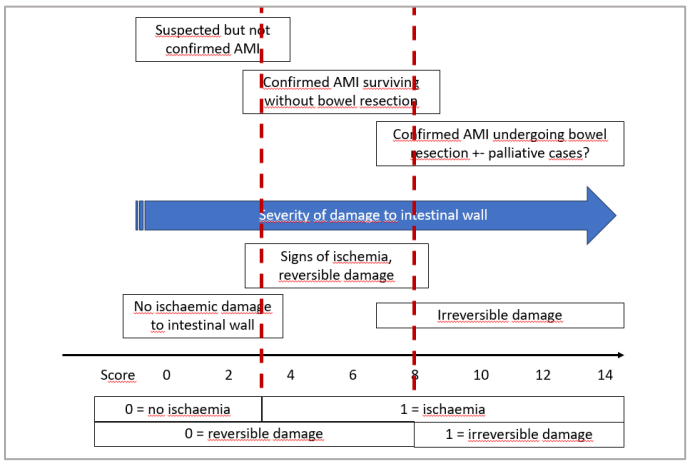


Figure 1. Conceptual approach for radiological score.

Pearson Chi-square or Fisher tests will be used for the comparison of categorical variables, and Student t-test or Wilcoxon rank-sum test for the comparison of continuous variables as appropriate.

All CT findings with a univariate p-value ≤ 0.1 were entered into a multivariate logistic regression model to gauge their independent association with non-salvageable bowel damage (comparison 1) or confirmed diagnosis of AMI (comparison 2). The radiological score will be constructed based on univariate logistic regression models, where the dependent variable will be non-salvageable bowel and the independent variable will be radiological sign. The number of models will be equal to the number of radiological signs. The coefficient from the model will be uprounded and used as a weight for the radiological sign. In case the weights from the univariate models are clinically not relevant, expert opinions will be used instead. All the radiological signs will then be multiplied with the assigned weights and then summed. Finally, one by one the radiological signs will be left out of the score to test, whether a simpler version of the score would also give as good results as the more complicated version. The goodness of the score will be evaluated using AUC. A similar score will be constructed for suspected vs confirmed AMI.

However, if this will not result in a useful score, we will use a more complicated approach based on interactions between the radiological signs and interpretations of the results from the simpler approach.

In the first approach, **two scores** will be constructed.

1) using data of all patients with confirmed AMI
2) using data of only patients with confirmed arterial occlusive AMI

The performance of these two score will be tested in the following cohorts:

a) all patients with confirmed AMI
b) only occlusive arterial AMI included
c) only non-occlusive AMI included
d) Patients with venous occlusive AMI excluded
e) Patients subjected to palliative care excluded

Table 1. Common radiological signs used to detect bowel ischaemia in CT imaging

	Radiological sign	**Description**
Vascular signs:		
1.	Occlusion of superior/inferior mesenteric artery/or its respective branches	No contrast enhancement on MDCT scan in the arterial phase or in the venous phase/lack of contrast enhancement within the vessel lumen / Acute arterial thrombi and emboli may appear as obvious low-attenuation filling defects in the SMA, its branches, or other major mesenteric arteries.
2.	Occlusion of superior mesenteric vein/or branches	No contrast enhancement on MDCT scan in porto-venous phase/lack of contrast enhancement within the vessel lumen / The thrombosed superior mesenteric vein is seen as a large, distended vessel that does not fill appropriately with contrast / a low-attenuation filling defect on contrast-enhanced CT.
Bowel signs:		
3.	Bowel dilatation	Abnormal dilatation of small or large bowel loops compared to the adjacent normal bowel loops. Evaluation of 3 different bowel segments is carried out – small bowel, large bowel and caecum. Abnormal dilatation is considered if the diameter is: - >30 mm for small bowel - >60 mm for large bowel - >90 mm for caecum Documentation of the findings: 1. No bowel dilatation 2. Unsure/uncertain/technically difficult to evaluate 3. Bowel dilatation present by radiologist assessment, specify the bowel segment

		4. Maximum bowel diameter in mm in three locations: small bowel, caecum large bowel, caecum Classification of the findings on bowel diameter will be worked out through the analysis of the results. First, cut-off values of bowel dilatation for prognostication of unsalvageable bowel for each segment under review will be identified. Second, Their weights will be identified and incorporated into the score.
4.	Decreased, absent or abnormal bowel wall enhancement	No contrast enhancement, segmental enhancement decrease of bowel loops in comparison with adjacent normally enhancing bowel loops or abnormal hyperenhancement of bowel loops. Documentation of the findings: 1. Normal bowel wall enhancement 2. Unsure/uncertain finding/technically difficult to evaluate 3. Hyperenhancement of the bowel wall 4. Decreased/diminished enhancement 5. No enhancement in the venous phase Evaluation of bowel wall enhancement will be documented in two different ways: 1. Small bowel, large bowel and caecum wall density is measured and documented in Hounsfield units (HU) 2. Visual evaluation of 4 quadrants of the abdomen and identifying visual differences of segmental bowel wall enhancement in comparison to adjacent bowel loops. If a difference is identified the segmental HU values are measured in visually normal and altered bowel loops. The significant difference is analysed further statistically.
5.	Pneumatosis intestinalis	Intramural small collections of gas in a segment of a small or large bowel. Documentation of the findings: 1. No pneumatosis intestinalis 2. Unsure/uncertain/technically difficult to evaluate 3. Possible pseudo-pneumatosis 4. Clearly detectable pneumatosis intestinalis
6.	Gas in the mesenteric or portal veins	Air collections inside the lumen of venous branches of vena mesenterica superior, inside of vena porta or its branches. Documentation of the findings: 1. No gas in mesenteric or portal veins 2. Unsure/uncertain/technically difficult to evaluate 3. Clearly detectable gas in mesenteric or portal veins

7.	Bowel wall thinning or thickening	Abnormal thinning of bowel wall compared to the adjacent normal bowel loops, “paper-thin wall” appearance. Changes in bowel wall thickness are documented in mm in three separate bowel segments. Abnormal thickness of the bowel wall is considered if: - small bowel wall >3 mm - colonic wall >1 - 2 mm (when the lumen is well distended) or >5 mm (when the wall is contracted or the lumen is collapsed) Documentation of the findings: 1. No paper-thin wall 2. Unsure/uncertain/technically difficult to evaluate 3. Paper-thin wall present by radiologist assessment 4. Max and min bowel wall thickness in mm in three locations: small bowel, caecum large bowel, caecum

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