ACUTE INTESTINAL NECROSIS: THE PREOPERATIVE DIAGNOSTIC APPROACH

PARTICULARLY REFERENCES TO ACUTE VASCULAR INTESTINAL NECROSIS

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BY
DAVID PIHL STRAARUP

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AALBORG UNIVERSITY
DENMARK

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II. Straarup D, Gotschalck KA, Christensen PA, Krarup H, Lundbye-Christensen S, Handberg A, Thorlacius-Ussing O. Exploring I-FABP, endothelin-1 and L-lactate as biomarkers of acute intestinal necrosis: a case-control study. Scand J Gastroenterol. 2023 Jul 4:1-7. doi: 10.1080/00365521.2023.2229930. Epub ahead of print. PMID: 37403410.

III. Rasmussen RW, Straarup D, Thorlacius-Ussing O, Handberg A, Christensen PA. Fully automatic d-lactate assay using a modified commercially available method. Scand J Clin Lab Invest. 2021 Jul;81(4):312-317. doi:10.1080/00365513.2021.1907859. Epub 2021 Apr 20. PMID: 33879006.

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V. 2: 2017 European Society of Coloproctology (ESCP) collaborating group. Safety of primary anastomosis following emergency left sided colorectal resection: an international, multi-centre prospective audit. Colorectal Dis. 2018 Sep;20 Suppl6:47-57. doi: 10.1111/codi.14373. PMID: 30255647.

VI. 3: 2017 and 2015 European Society of Coloproctology (ESCP) collaborating groups. The impact of conversion on the risk of major complication following laparoscopic colonic surgery: an international, multicentre prospective audit. Colorectal Dis. 2018 Sep;20 Suppl 6:69-89. doi: 10.1111/codi.14371. PMID:30255643.

VII. 4: 2017 European Society of Coloproctology (ESCP) collaborating group. Association of mechanical bowel preparation with oral antibiotics and anastomotic leak following left sided colorectal resection: an international, multi-centre, prospective audit. Colorectal Dis. 2018 Sep;20 Suppl 6:15-32. doi:10.1111/codi.14362. PMID: 30255646.

VIII. 5: 2017 European Society of Coloproctology (ESCP) collaborating group. An international multicentre prospective audit of elective rectal cancer surgery; operative approach versus outcome, including transanal total mesorectal excision (TaTME). Colorectal Dis. 2018 Sep;20 Suppl 6:33-46. doi: 10.1111/codi.14376. PMID: 30255642.

IX. 6: 2017 European Society of Coloproctology (ESCP) collaborating group. Evaluating the incidence of pathological complete response in current international rectal cancer practice: the barriers to widespread safe deferral of surgery. Colorectal Dis. 2018 Sep;20 Suppl 6:58-68. doi: 10.1111/codi.14361. PMID: 30255641.

ENGLISH SUMMARY

Acute intestinal necrosis (AIN) is a life-threatening disease due to diminished blood supply to a bowel segment. The mortality rate of AIN patients is above 50% despite continuing development in all relevant diagnostic modalities. The mortality rate is related to the short time span of approximately 6 hours between the obstructive event and the irreversible damage to the intestinal segment. No prodromal symptoms–nor severe abdominal pain are ubiquitous in AIN patients in this short initial phase. Additionally, radiological evaluation and blood-based parameters are characterized by unspecific findings. Overall, the necessary suspicion leading to immediate intervention might be hampered by unspecific clinical and paraclinical findings, which can further increase the mortality risk.

However, a quick diagnosis of AIN is reinforced by the patient´s medical history, objective clinical findings, abdominal computed tomography (CT) scan and blood-based parameters.

Despite reported sensitivity and specificity rates above 0.90 of abdominal CT scans focused on diagnosing AIN, the mortality rate remains roughly unchanged over decades. Additionally, no standard blood-based parameter or novel proposed AIN biomarker is reliable in diagnosing AIN.

The present study explores the diagnostic process in AIN patients with a focus on radiology and blood-based parameters.

Study one is a case–control setup illustrating radiological findings in unspecific preoperative abdominal CT scans in vascular AIN patients compared to acute unselected surgical control patients. One out of five AIN patients were scanned without intravenous contrast, and 3 out of 4 patients were not suspected to suffer from AIN at the initial clinical evaluation according to the radiological referral. The radiological findings of gastrointestinal vessel pathology, intestinal wall pathology, and intestinal diameter independently predict AIN. Additionally, subgroup analysis implied that increased contrast enhancement in the bowel wall, inferior mesenteric artery arteriosclerosis, pneumatosis intestinalis and colon contraction found on CT scans could predict AIN.

Study two explored the diagnostic performance of D-lactate as an AIN biomarker in a large cross-sectional case–control study. Serum D-lactate measurements in 44 AIN patients were compared to 2914 unselected surgical patients acutely referred to a department of gastrointestinal surgery due to abdominal pain. A minor proportion of the in-hospital patients were suspected to suffer from AIN. Due to lipemic interference, roughly half of the AIN and control patients were excluded from the analysis. A high-quality analysis of D-lactate in an automated analytical setup,

economically and practically fit for daily clinical practice, was developed. The diagnostic performance of D-lactate was found to be insufficient.

Study three investigated the diagnostic performance of intestinal fatty acid binding protein (I-FABP), endothelin-1 and L-lactate in 44 AIN patients compared to a group of age- and sex-balanced patients from the study two-cohort at a ratio of 1:5. Both I-FABP and, in particular, endothelin-1 showed promising diagnostic performance in diagnosing AIN. The combination of I-FABP and endothelin-1 did not add any further to the diagnosis of AIN. Finally, L-lactate was again rejected as a robust AIN biomarker.

In conclusion, survival after an AIN event is dependent on a quick diagnosis preferably followed by intervention within the first six hours. Several radiological findings are also independent diagnostic predictors of AIN in an unspecific abdominal CT scan in patients with a blurred clinical presentation. Standard blood-based parameters are unreliable as AIN biomarkers, including L-lactate. The proposed biomarker D-lactate is also rejected as an AIN biomarker, but I-FABP and, particularly, endothelin-1 showed promising diagnostic performance in patients admitted due to abdominal pain.

DANSK RESUME

Akut tarmnekrose (AT) er en livstruende sygdom, der skyldes manglende blodtilførsel til et eller flere tarmsegmenter. Dødeligheden hos AT-patienter er fortsat over 50% trods udvikling i alle relevante diagnostiske modaliteter. Det korte tidsrum på ca. 6 timer mellem ophørt blodtilførsel til tarmen og uoprettelig tarmskade er relateret til dødeligheden. Ingen prodromale symptomer er til stede hos hele gruppen af AT-patienter i denne korte indledede fase; heller ikke udtalte mavesmerter. Desuden er de radiologiske undersøgelsesfund samt blodprøvesvar ofte uspecifikke. Den vitale mistanke, der leder til umiddelbar behandling, er dermed hæmmet på grund af uspecifikke kliniske og parakliniske fund med en øget dødelighed til følge.

En hurtig diagnose af AT er baseret på anamnese, den objektive undersøgelse, CT-scannings fund samt blodprøvesvar.

På trods af at sensitivitet og specificitet af CT-scanningernes påvisning af AT er angivet til over 0.90, har mortaliteten stort set ikke ændret sig de seneste årtier. Yderligere, har hverken standardblodprøver eller nye blodprøve-biomarkører vist sig egnede til diagnostik af AT.

Studie 1 er et case-control-studie, som sammenligner fund på CT-scanninger hos patienter med vaskulær AT med uselekterede akutte kirurgiske patienter. Én ud af 5 patienter blev scannet uden intravenøs kontrast, og i 3 ud af 4 AT-patienter, var der ikke rejst mistanke om AT efter den initiale kliniske vurdering – bedømt ud fra den radiologiske henvisning. De radiologiske fund: Patologi i tarmens blodkar eller i tarmvæg samt tarmens diameter var uafhængige prædiktorer for AT. Yderligere detaljerede analyser antydede følgende prædiktorer for radiologisk påvisning af AIN: øget kontrastopladning i tarmvæggen, arteriosclerose i arterie mesenterica inferior, pneumatose i tarmvæggen samt kolonkontraktion.

Studie 2 undersøgte den diagnostiske kapacitet af D-laktat som en AT-biomarkør i et stort cross-sectional case-control studie. D-laktat blev analyseret på 44 AT-patienter samt på en stor gruppe kontrolpatienter. Kontrolgruppen på 2914 ikke-AT-patienter bestod af dels uselekterede kirurgiske kontrolpatienter henvist til en mave-tarm kirurgisk afdeling på grund af mavesmerter samt en mindre andel af indlagte patienter som mistænktes for AT. Grundet lipæmisk interferens måtte omkring halvdelen af blodprøverne fra AT-patienterne og kontrollerne ekskluderes fra analysen. Til analyserne udvikledes en højkvalitets analyse af D-laktat i et automatiseret analyse-setup, der såvel økonomisk som praktisk, ville kunne anvendes i det daglige kliniske arbejde. Imidlertid fandtes den diagnostiske værdi af D-laktat insufficient.

Studie 3 undersøgte den diagnostiske værdi af intestinal fedtsyre-bindende protein (I-FABP), endothelin-1 samt L-laktat i 44 AT-patienter kontrolleret mod en alders- og

køns-balanceret kontrolgruppe fra studie 2-cohorten i en 1:5 ratio. Både I-FABP, men særligt, endothelin-1 viste lovende diagnostisk kapacitet med hensyn til AT. Kombinationerne af disse markører gav ingen yderligere gevinst med henblik på en sikker diagnose. Undersøgelsen bekræftede desuden, at L-laktat er en upålidelig AT-biomarkør.

Overlevelse efter et AT-event er afhængig af en hurtig diagnose og behandling iværksat inden for de første ca. 6 timer. Med baggrund i ovennævnte studier konkluderes, at flere radiologiske fund på en uspecifik CT-scanning er uafhængige prædiktorer for AT hos patienter med uspecifikke kliniske fund. Standardblodprøver er ej heller pålidelige inclusive L-laktat. Den foreslåede biomarkør D-laktat kan, ud fra nærværende studie, ikke anbefales som AT-biomarkør, mens I-FABP og særligt, endothelin-1 viser lovende resultater.

This thesis is based on the following papers:

I. Straarup, D; Gotschalck KA; Christensen PA; Krarup H; Lundbye-Christensen S; Handberg Aa; Thorlacius-Ussing O D, Gotschalck KA, Mikalone R, Thorlacius-Ussing O. Preoperative findings on non-specific CT in patients with primary acute intestinal ischemia: a case–control study. European Journal of Trauma and Emergency Surgery [Internet]. 2021;(0123456789). Available from: https://doi.org/10.1007/s00068-021-01741-w

II. Straarup, D; Gotschalck KA; Christensen PA; Rasmussen RW; Krarup H; Lundbye-Christensen S; Handberg Aa; Thorlacius-Ussing O. Exploring D-lactate as a biomarker for acute intestinal necrosis in 2958 patients: a prospective cross-sectional study. In review.

III. Straarup, D; Gotschalck, KA; Christensen, PA; Krarup, H; Lundbye-Christensen, S; Handberg, A; Thorlacius-Ussing, O. Exploring I-FABP, endothelin-1 and L-lactate as biomarkers of acute intestinal necrosis: a case-control study. Scand J Gastroenterol. 2023 Jul 4:1-7. doi: 10.1080/00365521.2023.2229930. Epub ahead of print. PMID: 37403410.

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Finally, I want to thank my fantastic family for loving me regardless of success or failure!

David Pihl Straarup, Aalborg 2023

ABBREVIATIONS

ACR	American College of Radiology Appropriateness Criteria
AIN	Acute intestinal necrosis
AUC	Area under the ROC Curve
CI	Confidence interval
CRP	C-reactive protein
CT	Computed Tomography
ESCP	European Society of Coloproctology
FATP-4	Fatty acid transport protein-4
Glut-5	Glucose transporter protein-5
I-FABP	Intestinal fatty-acid binding protein
IMA	Inferior mesenteric artery
MD	Medicinae Doctor
MR	Magnetic Resonance
N	Number
NOMI	Nonocclusive mesenteric ischemia
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operator characteristic
SD	Standard deviation
SE	Standard error
SMA	Superior mesenteric artery
TaTME	Transanal total mesorectal excision

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CHAPTER 1. INTRODUCTION

1.1. PREFACE

"…occlusion of the mesenteric vessels is apt to be regarded as one of those conditions of which diagnosis is impossible, the prognosis hopeless and the treatment almost useless."

A. J. Cokkinis, 1926(1)

Standing in a proud tradition of research with constant development in numerous medical fields, the feeling of "standing" is more appropriate than "progressing" regarding the research of *diagnosing* acute intestinal necrosis (AIN). After a century where the prognosis and treatment have evolved for AIN patients, the statement of Cokkinis remains painfully relevant due to the diagnostic process. The search for a blood-based biomarker has for decades been a desert walk. Similarly, despite "sensitivity and specificity rates of 1.00" of an abdominal CT scan with respect to AIN, no general change in mortality has occurred.

Growing from this painful experience in my own clinical work with AIN patients, this study is a humble supplement to the fight against its terribly high mortality rate.

This study explores radiological findings in the most difficult AIN patients and tries to settle research questions in some proposed blood-based biomarkers and to add support to other biomarker research through 3 studies in AIN patients.

1.2. INTRODUCTION TO ACUTE INTESTINAL NECROSIS

1.2.1. TERMINOLOGY

"Mesenteric ischaemia" is a widely used imprecise term for an intestinal segment suffering from diminished blood supply. Confusion exists between clinicians and pathologists due to the terminology in the field, and a major portion of the literature is done by clinicians. The definition of *necrosis* is "…the death of a tissue occurring in a living body and it is irreversible", as stated by Ferris et al. (2). *Ischaemia* is suffering tissue due to the reduction of blood supply and may be the precursor of necrosis.

When focusing on the term “mesenteric (ischaemia)” as a surgeon, the mesentery is only the tissue sustaining the intestine and not the part of interest despite the vasculature is supporting the intestine through the mesentery. Resection of a necrotic intestine leaving the ischaemic mesentery is not an error. This isolated intestinal resection leaving the mesentery resolves the clinical derouting of the patient. This isolated intestinal resection is practised in gastrointestinal surgery worldwide. Similarly, from a strict surgical point of view, “ischaemia” is only relevant in the acute surgical setting as a precursor to the pathological end stage – necrosis. The ischaemic intestine is left in situ and inspected at re-exploration to spare the intestine (3). Indeed, the ischaemic intestine is not meaningless in the sense that ischaemia can initiate revascularization considerations. From a surgical point of view, the intestine is the suffering tissue, and necrosis is the end stage to be avoided. This is the background for the terminology used in this study – acute intestinal necrosis (AIN).

1.2.2. CLASSIFICATION

Diminished blood flow to an intestinal segment can evolve acutely or chronically. There are similarities in the pathogenesis and general clinical presentation of patients with acute disease compared to patients suffering from chronic disease. The chronic disease rarely propagates to intestinal necrosis due to collateral vasculature, although a portion of the patients suffering from AIN might be preceded by a grade of chronic status (4). Chronic disease is beyond the scope of this study.

Acute intestinal necrosis is caused by intravascular occlusion (primary AIN or vascular AIN), extravascular obstruction (secondary AIN or nonvascular AIN) and nonocclusive mesenteric ischaemia (NOMI). Intravascular AIN is caused by arterial embolism, arterial thrombosis, or mesenteric venous thrombosis. NOMI is caused by the collapse of blood circulation primarily due to cardiac disease and vasoconstriction. Extravascular obstruction is caused by compression of the blood vessels. This compression is due to different pathological conditions in the abdomen, such as strangulation of the bowel, adhesions, and herniation.

1.2.3. VASCULATURE OF THE INTESTINE

The vasculature of the bowel has its origin in the primitive ventral segmental arteries during embryogenesis (5). Three of these arteries develop into the three main vessels in the abdomen, the coeliac artery, superior mesenteric artery (SMA) and inferior mesenteric artery (IMA), together named the splanchnic vessels (Figure 1-1). The coeliac artery supplies the foregut, including the duodenum, to the major duodenal papilla. The SMA supplies the midgut, which includes the duodenum distal to the major duodenal papilla, jejunum, ileum, caecum, ascending and 2/3 of the transverse colon. The IMA supplies the hindgut, which includes the distal 1/3 of the transverse colon, descending colon, sigmoid colon, and rectum. The latter is also supplied from the middle and inferior rectal arteries from the internal iliac artery (6). Collateral blood

flow from these tree main arteries (Arc of Riolan, superior and inferior pancreaticoduodenal arteries and Marginal artery of Drummond) supports neighbouring areas (Figure 1-2). The collateral vessels in the small intestine are more ample than those in the colon.

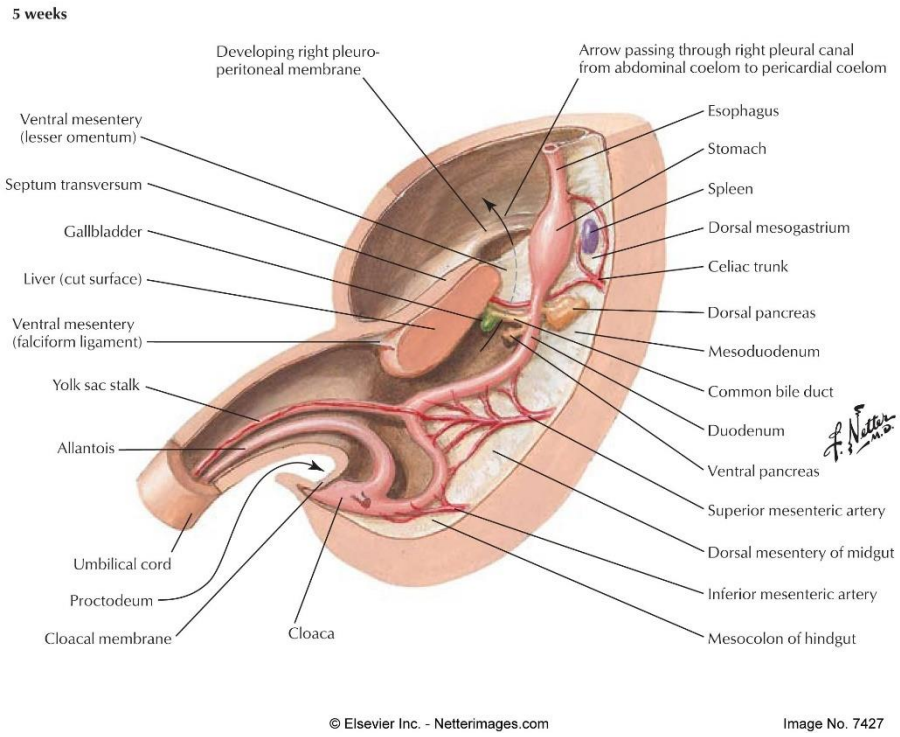

Figure 1-1: Development of the splanchnic vessels (5 weeks embryo) (Netter illustration used with permission of Elsevier Inc. All rights reserved. www.netterimages.com)(7).

The blood supply to the abdomen is abundant (5). 1/10 to 1/3 of the cardiac output is directed to the abdominal viscera, with 300–1200 mL per minute flowing through the SMA alone (5).

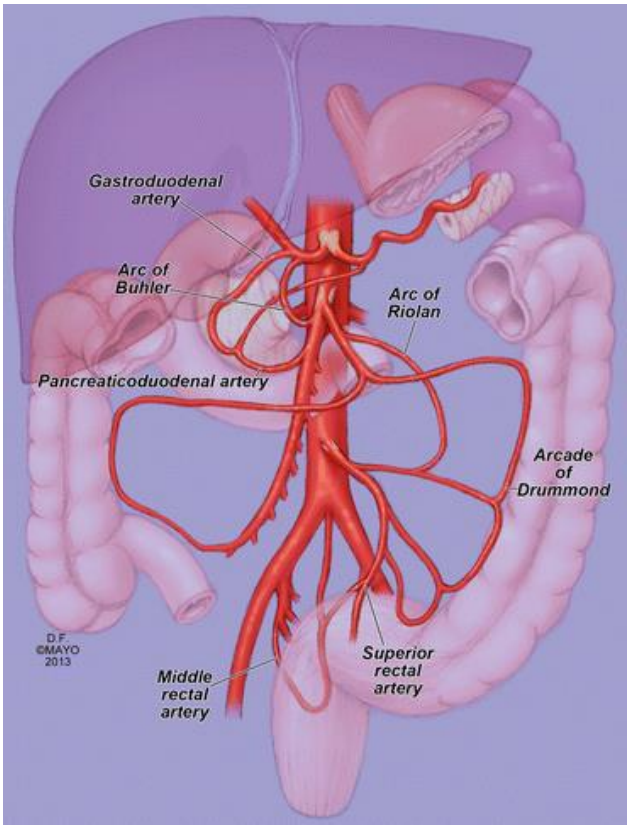

Figure 1-2: The splanchnic vessels of the abdomen, including collaterals (Reproduced with permission from Springer Nature)(8).

Venous drainage from the bowel is parallel to the arteries and empties into the portal vein (6).

1.2.4. PATHOPHYSIOLOGY

Insufficient delivery of oxygen and nutrients to maintain cellular metabolism is the cause of necrosis and cellular death of the intestinal segment. In fact, major intestinal damage is seen as early as 30 min after the obstructive event (9). A demolishing effect on the mucosal barrier in mucin and epithelial mucosal layers is accompanied by the destroying effect of proteases on the intestinal wall with an autodigestional effect (9). Finally, a devastating inflammatory response following cytotoxic mediator action is, when untreated, succeeded by death of the patient (9). However, collateral blood flow and increased oxygen extraction can maintain cell metabolism for hours depending on the extent of the vascular affection. In complete occlusion, the ischaemia will turn into necrosis in approximately six hours (10).

1.2.5. AETIOLOGY AND RISK FACTORS

Every condition in the abdomen resulting in diminished blood flow can cause necrosis.

The main aetiologies for AIN are, as mentioned, extravascular obstruction and intravascular occlusion of the blood flow (11–13). Extravascular obstruction is due to compression or an intestinal twist, for instance, a herniation with entrapment of an intestinal segment or an intestinal volvulus. Stasis and/or diminished arterial inflow causes necrosis. Thus, nonvascular AIN risk factors are sequelae from earlier surgery with adhesion formation, herniations in old scars and other conditions compressing the arterial inflow or venous outflow.

Arterial intravascular occlusion and NOMI due to diminished arterial inflow cause the same impairment of cellular metabolism, although engorgement in the venous system is absent in contrast to venous occlusion. Intravascular occlusion accounts for over 2/3 of AIN cases and is either caused by arterial embolism (50%) or thrombosis (15-25%) at a ratio of approximately 1.4:1 in regard to SMA (14,15). Mesenterial venous occlusion accounts for 5% and NOMI for 20%–30% of AIN cases (15). Thus, arterial embolism is the dominant aetiology in intravascular AIN, and SMA is the primary vessel involved. Arterial embolus is more prone to affect the SMA due to the oblique origin of this vessel (Figure 1-3) (16). An embolus in the proximal 10 centimetres of SMA occluding the blood flow to the whole small intestine is encountered in 15% of SMA occlusions and can cause the death of the patient if left untreated (17).

Arterial thrombosis is a part of the universal arteriosclerotic burden in primarily older patients with acute closure of a stenotic part of the vessel. The arterial thrombotic occlusion affecting the SMA might cause limited damage due to well-developed collaterals. Thus, affection of at least two of the tree splanchnic vessels is considered mandatory to cause an AIN event (18).

Thromboembolic risk factors predisposing *vascular* AIN include atrial fibrillation, recent myocardial infarction, congestive heart failure, or peripheral arterial emboli (19). Additionally, arteriosclerotic plaques in the splanchnic vessels and the aorta or recent cardiac or vascular surgery may predispose patient to vascular AIN (20,21). Risk factors predisposing arterial *thrombosis* include chronic mesenteric ischaemia symptoms and, a history of coronary artery disease, peripheral artery disease and tobacco use (21).

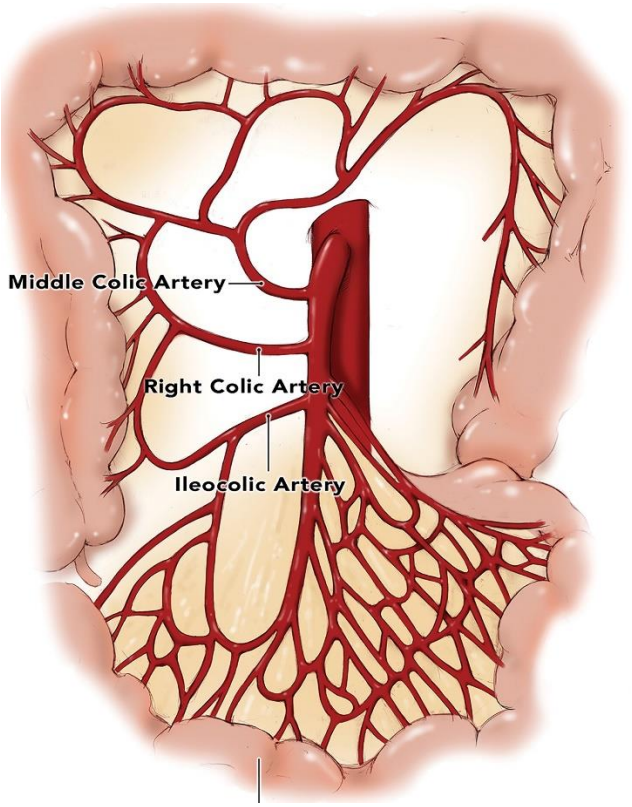

Figure 1-3: Superior mesenteric artery (Reproduced with permission from RSNA: Ghodasara et al. RadioGraphics 2019; 39:559–*577)* (22).

Venous thrombosis originates from idiopathic diseases such as thrombophilia or from secondary causes such as surgery, medication, injury, inflammation, venous stasis or malignancy (21). The treatment is primarily conservative and venous thrombosis is a rare course of AIN.

NOMI is due to circulatory collapse and extreme vascular contraction and primarily seen in intensive care during treatment with massive vasopressor agents. The necrotic development is the same as in arterial intravascular occlusion, although the development is more protracted. Thus, NOMI risk factors are recent cardiac surgery, end-stage renal disease, congestive heart failure, Digitalis use, massive vasopressor use or extreme hypovolemia (21).

1.2.6. EPIDEMIOLOGY

AIN incidence has been reported with great uncertainty over the past decade. Older data from Sweden showed AIN due to SMA occlusion in 0.9% of all autopsies with an autopsy rate of 87% (14). A recent meta-analysis reported an incidence of 6.2 cases pr. 100.000 person-years, and approximately 0.05% of hospital admissions are related to AIN (23).

The risk of AIN has classically been reported to be strongly related to sex and age (19). Nevertheless, Acosta et al. showed in their population-based study that age-standardized incidence is equal for both sexes (24). However, they reported 66% females out of 213 AIN cases from 1970-1982. Additionally, the incidence exponentially increased with age above approximately 65 years in the same study, where the median age was reported to be 81 years.

1.2.7. PROGNOSIS

The one-year mortality of AIN remains above 60% despite improvement in multiple medical specialties, including the development of intravascular treatment (24), although some improvement has been reported in the last 2 decades (23). A recent meta-analysis reported pooled mid-term and long-term mortality (>6 months to 5 years) for AIN of 68.2% (95% confidence interval (CI) 60.7;74.9) (23). The 1-year mortality in a large nationwide retrospective study of 161 revascularized patients treated with open revascularizing surgery in the period from 1999 to 2006 was 59% (25). Mortality in relation to the aetiology was also reported by Tamme et al. and showed large differences. Thus, the thirty-day mortality of NOMI is reported as 58.4% (95% CI: 48.6; 67.7), the thirty-day mortality of mesenterial venous thrombosis is 24.6% (95% CI 17.0; 32.9) and the thirty-day mortality of occlusive arterial AIN is 51.8% (95% CI 46.3; 57.3) (23). Different prognostic factors of mortality have been reported. A recent meta-analysis identified 33 factors predicting mortality in AIN patients, including chronic renal disease, cardiac failure, hypotension and inotrope administration and delay to surgery (25).

CHAPTER 2. DIAGNOSIS

2.1. DIAGNOSTIC CHALLENGES

Irreversible intestinal necrosis due to a total obstruction of blood supply develops approximately six hours after the occluding event (10). This time pressure demands efficient diagnostic tools. The tools used include the patient´s medical history, clinical examination, blood-based parameters, and radiological examinations. Each of these steps present a challenge.

The objective signs of AIN in the first clinical evaluation are frequently vague and may prevent the initiation of the clinical suspicion of AIN. A retrospective study from France showed that no peritoneal signs were found in 85% of AIN patients upon initial examination (26).

The initial lack of suspicion potentially results in a time–consuming paraclinical workup or admission of the patient to observation and secondary evaluation, which may result in clinical derouting. Time–consuming examinations might include an abdominal CT scan. Nevertheless, the radiological report is compromised when a specific suspicion of AIN is not mentioned in the radiological referral (20).

This impaired clinical suspicion has also affected AIN research. A major bulk of the studies in AIN patients include only individuals *suspected* to suffer from AIN (27–33). Thus, research in the most difficult patients with vague objective findings and no evoked suspicion of AIN is roughly absent in prospective research.

When the suspicion of AIN is finally raised, the clinical derouting may have emerged, making consent to research difficult or even ethically questionable, resulting in a scarcity of recruited patients to a potential study. This problem challenges AIN research in acute unselected patients everywhere, as exemplified in the study by Ofer et al. from 2009 (29). Patients in this study were included if they met certain criteria, including the classical “pain out of proportion to objective findings” and other parameters, such as metabolic acidosis or atrial fibrillation. Interestingly, they included unconscious patients without consent. However, even including unconscious patients suspected to suffer from AIN and harvesting patients with a broad range of AIN disposing factors, only 18 of the 93 patients (19%) suffered from AIN (study period 16 months). This also highlights the problem with research in a rare disease as well as the weaknesses tied to anamnestic findings such as disposing factors.

Thus, useful research giving clear answers and advices in diagnosing AIN are hampered by several compromising factors, such as low inclusion rate and selection bias ignoring parts of the AIN patients.

Nevertheless, clinicians are in desperate need of tools that can help evoke suspicion in patients with vague or even no symptoms.

Radiological examinations requested for patients with a “blurred” clinical picture might aid in this process if the early radiological signs of AIN are known.

Moreover, blood-based biomarkers might also provide valuable alerts in resemblance to, for instance, elevated coronary enzymes in cardiac thromboembolic events.

In brief, radiological examinations and blood-based parameters are the tools used to diagnose AIN, and their refinement and development are highly needed.

2.2. CLINICAL PRESENTATION

The clinical presentation of the patient is closely related to the aetiology and time span from the acute event. Acute onset of abdominal pain has classically been accepted as a prodromal symptom (34). This pain accompanied by nausea and vomiting is severe and contrasts the objective findings (35). However, this is far from a ubiquitous clinical picture, but in the pure form, vascular AIN must be considered.

Chronic mesenterial ischemia is more classical with postprandial abdominal pain and anorexia with weight-loss, even though the picture is very variable (34).

Objective findings of nonvascular AIN are strictly correlated to the obstructive pathology and accompanied by ubiquitous subjective intense pain. Intestinal obstruction due to adherences causes nausea and vomiting and distended abdomen, whereas an entrapped intestine in a hernia is accompanied by a visible, red, and warm bulge.

Bloody diarrhoea and abdominal pain might accompany colon ischaemia or necrosis.

2.3. REFERENCE STANDARDS

Surgery with intestinal resection followed by histological verification is stated as the gold standard (12). However, even intraoperative evaluation of the viability of the intestine is questionable (36). Nevertheless, both radiological and surgical signs have been used as endpoints in some studies, casting doubt on the results (35–37). Conventionally, angiography has been historically seen as the gold standard (28), but an occluded vessel might be present even in the viable intestine due to collateral perfusion, although, 2 out of 3 occluded splanchnic vessels are a prodromal sign of AIN (29).

2.4. COMPUTED TOMOGRAPHY SCAN

The computed tomography (CT) scan is the radiological modality of choice in the initial evaluation of an acute patient due to accessibility, time consumption and quality (38,39). The magnetic resonance (MR) scan is more time-consuming and not a relevant alternative in the acute setting for examining patients with abdominal pain (39,40). Furthermore, the MR scan adds no additional information compared to CT scans in the porto-venous phase (41). Angiography has been the reference standard but, due to its low accessibility and time consumption, is reserved for therapeutic manoeuvres (39).

2.4.1. INTRAVENOUS CONTRAST ENHANCEMENT

The American College of Radiology Appropriateness Criteria (ACR) recommends early CT scans with intravenous contrast enhancement (39). Unenhanced CT scans due to compromised renal function are an independent prognostic factor for in-hospital mortality (42). Nevertheless, renal impairment is widely used as a contraindication to intravenous contrast enhancement, compromising the CT scanning quality, and has been shown to be of minor importance (43–46). Acosta et al. found in a retrospective study of 55 patients suffering from acute SMA occlusion no mortality or need for dialysis even after endovascular intervention and an initial diagnostic abdominal CT with intravenous contrast (43). Additionally, the mortality rate in patients receiving intravenous contrast does not increase due to contrast use (45). Nevertheless, a portion of the literature still reports considerable noncontrast scanning rates, probably incompletely explained by patient allergies to the contrast medium. Thus, Mazzei et al. performed a retrospective study in 34 patients confirmed to suffer from AIN. Fourteen percent were noncontrast CT scans (47). Inclusion criteria in their study was confirmation of AIN by angiography alone. This might, however, introduce selection bias. Nevertheless, their noncontrast CT scan rates were still considerable. Verdot et al. researched transmural necrosis in NOMI patients (48). They excluded 25 noncontrast CT scans from the study (11%). In other words, research in AIN patients is hampered by the exclusion of patients with noncontrast abdominal CT scans alone (48), weakening the potential conclusions concerning noncontrast CT scans. Altogether, suspecting AIN and being in favour of an early diagnosis outweighs the potential of contrast-induced nephropathy (49).

2.4.2. ORAL CONTRAST

Oral contrast is abandoned in the initial acute setting CT scan for several reasons: first, the risk of aspiration is not negligible in acute patients; second, the ischaemic intestine must be paralytic and hence, excludes the relevant intestinal segment of visualization; third, high-density contrast creates artifacts impairing sufficient examination quality; and fourth, waiting for the indigestion of contrast costs valuable time in the diagnostic workup (39,50).

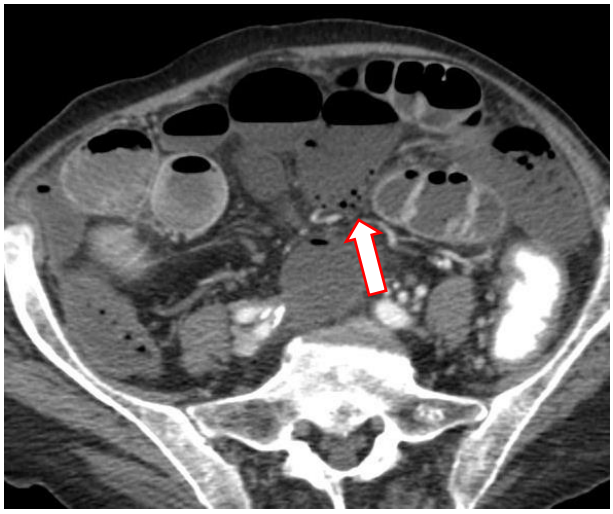

Figure 2-1: Pneumatosis intestinalis (arrow) with poorly enhanced bowel wall in a patient suffering from AIN in the small intestine and right colon.

2.4.3. CONTRAST PHASES AND DIAGNOSTIC PERFORMANCE OF A CT SCAN

Triphasic CT scans consist of an unenhanced scanning phase and an arterial and a portal venous phase and are the most comprehensive scanning modality in the average abdominal CT scan. Nevertheless, it is well documented that the unenhanced phase can be left out without compromising the diagnostic performance while simultaneously reducing the radiation dose (28,29,39,50–54). The specificity and sensitivity of a CT scan in the last century were reported to be above 0.90 if at least one of the following signs were present: arterial or venous thrombosis, pneumatosis (Figure 2.1), or solid organ infarction (55). In recent decades, studies have repeatedly reported sensitivity and specificity for CT scans with respect to AIN of above 0.90, particularly in patients *suspected* to be experiencing AIN; thus, patients are offered an optimal CT scanning protocol with intravenous contrast (12,56).

2.4.4. RADIATION EXPOSURE

Radiation doses and related cancer risk are a point of debate in the literature (57–61). Cancer risk has classically been estimated from major exposures such as the Chernobyl and Hiroshima catastrophes (62). Recently, JAMA Surgery published a population-based study from South Korea concluding that the radiation dose from abdominal CT scans performed in a perioperative time window related to appendectomies gives a higher incidence of haematologic cancer (63). They also reported an increased rate of abdominal CT scans related to this indication from 10.7%

to 45.1% from 2005 to 2015. Additionally, the study reported an absolute excess incidence rate of haematologic cancers of 4.44 (95% CI: 1.83; 6.70)/100 000 person-years. Moreover, there was no increased risk of other malignancies. Finally, the authors suggested that newer scanners might reduce the radiation dose.

Altogether, radiation exposure is a relevant concern, but it is generally accepted that a pertinent medical indication justifies the risk of future cancers (64). AIN is a deadly disease predominantly seen in older patients, making the examination indication weighty compared to radiation exposure concerns.

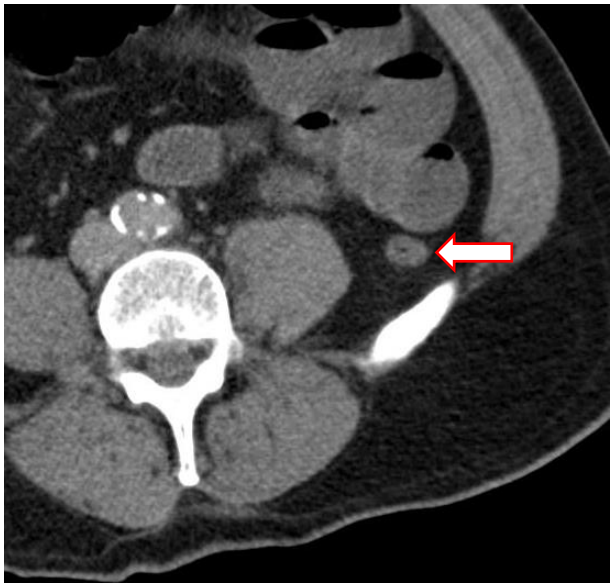

Figure 2-2: Colon contraction (arrow) in a patient suffering from AIN in the small intestine.

2.4.5. PATHOLOGICAL RADIOLOGIC FINDINGS IN AIN

CT findings in AIN patients can be classified in different ways. Specific or nonspecific findings due to AIN are one of the classical ways to categorize pathological findings in CT scans. Nevertheless, time relation plays a crucial role in pathogenesis and disease management, making it relevant to specify the findings on CT in early, intermediate, and late signs with respect to the time-dependent development of the disease. As mentioned, arterial vascular occlusion is the most challenging AIN subtype to diagnose and the main focus of the following section. A number of AIN-related findings on CT scans addressed in the literature are listed in Table 2-1.

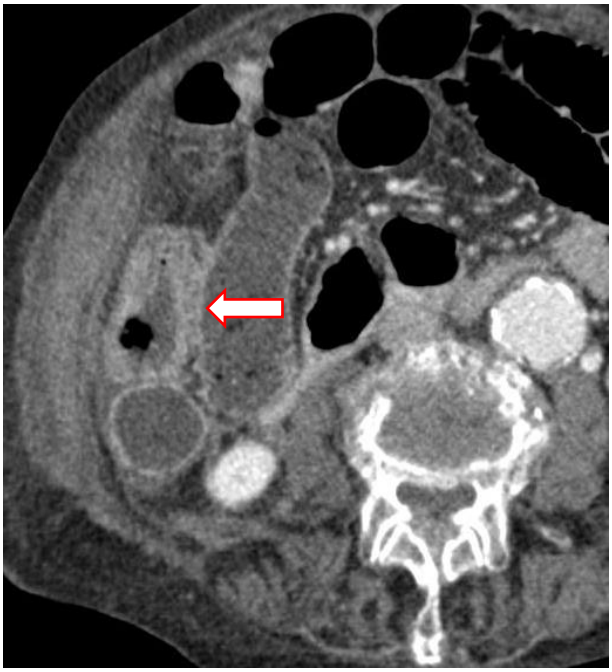

Figure 2-3: Increased contrast enhancement (arrow) in the bowel wall in a patient suffering from AIN in the coecum.

2.4.5.1 Early radiological signs

Vascular occlusion emerges with arterial filling defects on contrast enhanced CT scans, potentially with direct radiological visualization of the embolus. The bowel is contracted due to neurogenic spastic reflex (Figure 2-2), and the wall emerges unenhanced or poorly enhanced (Figure 2-1). This spastic phase is estimated to extend for 3-4 hours (65–67).

2.4.5.2. Intermediate radiological signs

The hypotonic ileus succeeds the spastic ileus, showing a dilated intestine with loss of muscle tone, and reduced vessel and tissue volume, and the intestinal wall might appear paper-thin. Intestinal wall haemorrhage and oedema follow in about 8-10 hours (65,67).

2.4.5.3. Late radiological signs

In the following hours, evidence of necrosis is seen with signs such as ascites, mesenteric pneumatosis (Figure 2-1), portovenous gas and potentially free intra-abdominal air as a sign of perforation (65,67).

Table 2-1: AIN pathology related to radiologic findings, time relation and specificity.

	Proposed pathology	*Time relation*			*AIN specific*		*References*
		Early	*Intermediate*	*Late*	*Specific*	*Nonspecific*	
Vascular:							
Affection of 2/3 coeliac vessels						X	(68)
Arterial filing defects		X			X		(40,69–71)
Arterial stenosis							(72)
Calcification							(40)
Venous engorgement							(73)
Portal venous gas	Transmural necrosis			X	X		(30,53–55,70,74–76)
Thromboembolic occlusion		X			X		(28,29,40,55)
Vein thrombosis		X					(28)
Bowel wall:							
Absent enhancement	Obstructed blood supply	X			X		(70,71,73,75,77–80)
Dilatation	Hypotone ileus		X	X		X	(54,68,74,75)
Halo-sign	Enhanced mucosa. Nonenhanced submucosal layers.						(40,70,81)
Hyperattenuation	No contrast: haemorrhage. Contrast: congest./reperfusion	X	X			X	(40,70,81)
Hypo-attenuation		X					(69,81)
Increased enhancement						X	(68)

	Proposed pathology	*Time relation*			*AIN specific*		*References*
		Early	*Intermediate*	*Late*	*Specific*	*Nonspecific*	
Pneumatosis intestinalis	Transmural necrosis			X	X		(53,54,70–72,75,81,82)
Thickening	Oedema, haemorrhage, stasis	X	X			X	(29,40,54,66,68,70,71,73,74,77,81)
Thinning	Loss of tissue and vessel volume and muscle tone		X	X			(66,70,75,81)
Other:							
Intestinal contraction	Spastic reflex ileus	X					(78,83)
Intestinal dilatation			X				(83,84)
Mesenteric fat stranding	Congestion or reperfusion		X	X		X	(29,68,70,77)
Mesenteric oedema							(40,73)
Peritoneal fluid						X	(40,54,68,73,74,78)
Pneumoperitoneum				X		X	(68,81)
Small bowel faces sign							(73)
Solid organ infarction						X	(68,85)

2.5. BLOOD-BASED PARAMETERS

The classical definition of a biomarker by the World Health Organization is “any substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease” (86). Following this definition, a useful AIN blood-based biomarker must fulfil certain criteria and at least the following: First, a biomarker must have a relevant concentration change due to ischaemic circumstances in the intestinal environment. Second, the biomarker concentration must be detectable in the sampling site, ideally a venous blood sample. This includes a very important passage of the liver without notable elimination and elimination in the kidneys that is not too aggressive. Third, the biomarker needs to be detectable in a routine laboratory. Finally, the biomarker must be stable and inexpensive to analyse.

2.5.1. STANDARD BLOOD-BASED PARAMETERS

Diagnosis of AIN in the clinical setting is, as mentioned, supported by the patient´s medical history, clinical and radiologic examination, and biochemical tests. Several standard blood-based parameters are used in the initial clinical evaluation of patients suspected to suffer from AIN, although the evidence is scarce or conflicting. No standard blood-based parameter has reached sufficient diagnostic performance to qualify as an AIN biomarker. Several parameters have, however, been evaluated due to AIN diagnosis, and the most frequently researched are listed in Table 2-2.

The acute phase reactant C-reactive protein (CRP) and the general inflammation marker white blood cell count are widely used as cornerstones in the acute evaluation of patients with abdominal pain. CRP is a marker of infection and a direct measure of inflammation (87). The half-life is constant in health and disease; thus, the plasma concentration is only related to the production rate. Moreover, the increase in CRP concentration starts early after four to six hours (88). Kärkkäinen reports on a case series of 37 patients suffering from AIN due to arteriosclerotic arterial disease where every patient had CRP elevation that was typically above 100 mg/L. Similarly, the white blood cell count was elevated in all patients and typically in the range of 11 to $19x10^9$/L (20,89). Nevertheless, CRP elevation fails to differentiate acute care patients according to aetiology and may be evaluated in conjunction with other parameters (90).

In their recent review, Khan et al. evaluated different standard blood-based parameters according to a future scoring system for AIN and provided support for D-dimer and aspartate aminotransferase, with the latter in only NOMI patients (91). Moreover, they propose a few newly reported parameters including “Neutrophil to Lymphocyte Ratio” and “Red Cell Distribution Width” as well as D-lactate (91).

D-dimer attracts particular attention. An observational study in The British Journal of Surgery from 2004 reported D-dimer as the only significantly elevated blood-based parameter in nine SMA-occluded AIN patients (92). The sensitivity and specificity with a cut-off of 0.3 mg/L were 1.00 and 0.26, respectively. Additionally, the negative predictive value was reported to be 1.00 and has been repeatedly confirmed. A meta-analysis found a pooled sensitivity for D-dimer of 0.96 and specificity of 0.40 (56).

In conclusion, no standard biomarker reaches sufficient diagnostic performance to diagnose AIN, but a single standard parameter might attract attention in combination with other parameters. For instance, exploiting the high sensitivity and negative predictive value of D-dimer. Several proposed blood-based biomarkers are displayed in Table 2-2.

2.5.1.1. L-lactate

In need of a better parameter, L-lactate can be considered. L-lactate is the most widely used classical AIN biomarker and was introduced into clinical practice during the 1970s (93,94). The triad of elevated L-lactate, white blood cell count and abdominal pain has for decades been a classical dogma of the clinical and paraclinical picture of an AIN patient (95,96).

L-lactate is one of the enantiomers of lactate and the end product of anaerobic glycolysis, which is metabolized to pyruvate by lactate dehydrogenase, everywhere in the human body (97). L-lactate is abundantly metabolized in the liver and excreted by the kidneys. L-lactate elevation is a sign of compromised metabolism, systemic hypoperfusion and hypoxemia and is further seen in circulatory shock, liver coma, acute pancreatitis, diabetic ketoacidosis, and renal failure; in AIN, it might be elevated during the course of the disease (13,96,98). Considerably elevated L-lactate is not specific for AIN but suggests that the patient is in imminent danger of life (95).

The literature on L-lactate contains heterogenic conclusions on its use as an AIN biomarker. In recent decades, experimental (99,100) or human studies have supported the use of L-lactate as an AIN biomarker in selected patient groups, such as patients with reconstructed abdominal aorta (101) or in other specific AIN subgroups (102–104). Another group of L-lactate researchers speculated that L-lactate could support the diagnostic process (105–107) or that their results call for further research (108). Nevertheless, a growing body of experimental (98) and human studies (109–114) as well as a number of reviews (21,26,68,93,94,97,115–119), meta-analyses (56) and clinical guidelines (13,120–122) have rejected L-lactate as a reliable biomarker for diagnosing AIN, and some even claim L-lactate as a potential diagnostic pitfall (123).

2.5.2. NOVEL BLOOD-BASED PARAMETERS

AIN biomarkers have been sought for decades. No novel biomarker has reached the clinical setting despite comprehensive efforts (Table 2-2).

2.5.2.1. D-lactate

D-lactate, one of the novel proposed blood-based biomarkers of AIN, is the stereoisomer of L-lactate. Literature concerning D-lactate acidosis in humans was introduced in 1979 (124). However, D-lactate elevation in AIN patients is at a considerably lower level < 1 mM (125). In contrast to L-lactate, D-lactate is found in low quantities in the human body and is primarily produced by lactic acid bacteria in the intestinal lumen (126). Additionally, some D-lactate might originate from the ingestion of preformed D-lactate (Yoghurt and sauerkraut) and through metabolism in the human mitochondrial methylglyoxal pathway (in diabetic ketoacidosis or through exposure to propylene glycol; a solvent in a variety of food and in several intravenous medications) (127).

In theory, D-lactate has some characteristics that might qualify it as a potential AIN biomarker. First, the acidic environment in the ischaemic intestine results in bacterial overgrowth by D-lactate-producing bacteria (127). Second, lactic acid bacteria increase their production of D-lactate under anaerobic conditions (127). Third, the lowering pH in the acidic environment increases the absorption of D-lactate from the intestinal lumen to cause hyper-D-lactatemia (127). Fourth, translocation of D-lactate through the diseased intestinal wall has been demonstrated (128). Fifth, the main site of D-lactate production is in the intestine (129). Sixth, one can speculate that translocation might introduce D-lactate to the systemic circulation causing escape from metabolization in the liver, and sending D-lactate to a potential peripheral sampling site.

Doubt has been raised concerning hepatic elimination. From the statement of total absence of hepatic elimination in humans in the 1980s up to the 2010s (129), it has been demonstrated that D-lactate is degraded in several tissues, including the liver, by the so-called D-LDH or D-alpha carboxy acid dehydrogenase, which is distinct in structure and function from L-lactic acid dehydrogenase (126,127,130,131). Elimination through the kidneys is low at low plasma concentrations but rises with increasing plasma concentration (127).

D-lactate has been proposed as one of the most promising AIN biomarkers. Several studies, experimental (132) as well as human studies (108,126,129,133,134), support this prospect. In the study by Shi et al., D-lactate was proposed as a potential biomarker for disease severity in AIN patients, and the average D-lactate concentration was significantly higher in AIN patients who died because of the AIN event (n=14) than in AIN patients who survived (n=25)(129). Several reviews have the same conclusion (97,135). Other studies proposed that D-lactate is useful in a broader context, such as an early marker of gastrointestinal complications after cardiac surgery (125). A clinical guideline concludes that D-lactate may have potential as an early diagnostic tool in AIN (121). Nevertheless, some experimental (136) and human studies (137,138) as well as reviews (139,140) have shown disappointing results. A meta-analysis from 2017 states that the included studies are

heterogeneous and have small patient populations, resulting in “summary sensitivity and specificity being relatively low” and “must be interpreted with caution” (141). The guidelines for the World Society of Emergency Surgery exclude biochemical parameters, including D-lactate, in the diagnosis of AIN due to insufficient accuracy (120). Additionally, other studies fail to show a benefit of D-lactate to discriminate AIN from control patients but suggest that it might be useful to predict survival after intestinal resection (142). Finally, one study show significantly elevated D-lactate but conclude that further research is warranted (108). In summary, more studies on D-lactate use in AIN patients are warranted.

2.5.2.2. Intestinal fatty acid-binding protein

In the mid-1970s, a soluble fatty acid-binding protein was identified in the intestinal mucosa and other tissues in rodents (143). A decade later, the human intestinal fatty-acid binding protein (I-FABP) genes were described (144), and in the early 1990s, I-FABP was proposed as a useful AIN biomarker in experimental (145,145) and human studies (146).

I-FABP is a small protein that is abundant in the cytosol of mature enterocytes in the small bowel from the duodenum to the ileum (147). In intestinal ischaemia and intestinal barrier disintegration, I-FABP is released into the circulation (146,148).

Since the 1990s, research on I-FABP in humans (110,146,147) has supported the promising results of I-FABP as an AIN biomarker. I-FABP has also been proposed as an *early* AIN biomarker (149). I-FABP has been tested with promising results in different patient subgroups, such as AIN in patients undergoing open aortic repair (149) and AIN with particular reference to vascular AIN (147) and NOMI patients (150). A meta-analysis from 2016 summarized 9 studies and found a pooled sensitivity of 0.80 (95% CI: 0.72; 0.86) and a pooled specificity of 0.85 (95% CI: 0.73; 0.93), concluding that I-FABP may be a useful tool to diagnose AIN (151). The guidelines of the World Society of Emergency Surgery commented on the conflicting evidence on I-FABP and omitted any recommendations concerning I-FABP (120). Finally, research has also directly questioned I-FABP as an AIN biomarker (137).

2.5.2.3. Endothelin-1

One of the most potent and long-lasting vasoconstrictors known was discovered in the early 1980s and named endothelin-1. In the late 1980s, it was described and gene sequenced (152). Extensive research has been performed since, uncovering the effect of endothelin in almost all human tissues, including the vasculature, lung, heart and kidneys, with regulatory function on the autoimmune and endocrine system, as well as in obesity (153). Endothelin-1 is known to be elevated in patients with terminal renal failure, essential hypertension, myocardial infarction, cardiac failure, and pulmonary hypertension (154). Endothelin-1 is a small multifunctional peptide and produced by a broad range of human cells, including endothelial cells and smooth muscle cells (153).

The vasoconstrictor effect of endothelin-1 is also potent in the splanchnic vessels and part of the regulation of the circulatory system, mirroring the fluctuation between fasting and nutrition (5). Experimental studies have shown that impaired intestinal microvascular perfusion in the distal jejunum and ileum in patients undergoing cardiopulmonary bypass may be mediated by endothelin-1 (155). Additionally, it is speculated that endothelin-1 plays a role in persistent vasospasm in AIN after revascularization (156). Equally important, endothelin-1 research has also uncovered antiapoptotic effects with a cell protective effect in vascular smooth muscle cells (157–159). Nevertheless, proapoptotic effects of endotholin-1 have also been demonstrated (160). The relationship between the apoptotic effect and AIN remains unclear.

Endothelin-1 research with respect to AIN is scarce and consists of a few experimental studies (including the above studies) and one human study in NOMI patients. A study in rats proposed endothelin-1 as a potential biomarker of AIN (161). After 30 minutes of intestinal ischaemia, endothelin-1 was significantly elevated. In a study in pigs, endothelin-1 elevation followed vascular occlusion (162). Groesdonk et al. performed the only clinical study in AIN patients (154). In this study, endothelin-1 elevation was found to be a risk factor for NOMI in 78 AIN patients out of 865 patients undergoing elective cardiac surgery with extracorporeal circulation. Even preoperative elevation of endothelin-1 was related to postoperative NOMI (154).

Table 2-2: Blood-based parameters proposed as AIN biomarkers displaied with diagnostic performance.

Parameter	*AUC*	*Sensitivity*	*Specificity*	*References*
Alanine aminotransferase		0.73	0.60	(91)
Alkaline phosphatase		0.80	0.64	(91)
Alpha glutathione transferase		0.72	0.77	(163)
Amylase		0.38 (0.25–0.50)(91)	0.67 (0.63–0.71)(91)	
Aspartate aminotransferase	0.80 (147)	0.70 (0.64–0.75)(91)	0.73 (0.50–0.96)(91)	
Base-deficit	0.67 (147)			
CRP	0.74			(147)
D-dimer	0.74 (147)	0.96 (0.89–0.99)(56)	0.40 (0.33–0.47)(56)	
D-lactate		0.78 (0.38–0.90)(91)	0.86 (0.23–1.00)(91)	
Endothelin-1		0.51 (154)	0.94 (154)	
Fatty acid transport protein-4				(164,165)
Glucose transport protein-5				(166)
I-FABP	0.88 (147)	0.83 (147)	0.89 (147)	
Ischaemia-modified albumin				(167,168)
Lactate dehydrogenase	0.78 (147)	0.70 (0.62–0.92)(91)	0.49 (0.43–0.77)(91)	
Leukocyte count, 10^9/L	0.54 (0.39–0.70)(147)	0.82 (0.57–0.90)(91)	0.58 (0.37–1.00)(91)	
L-lactate		0.69 (0.33–0.88)(91)	0.76 (0.48–0.96)(91)	(147)
Neutrophil to lymphocyte ratio		0.74 (0.74–0.74)	0.86 (0.83–0.89)	(91)
Red cell distribution width		0.67 (0.48–0.69)	0.82 (0.63–0.89)	(91)

Range in parenthesis is 95% confidence intervals. A single number parentheses is a literature reference. AUC: Area under the receiver operator characteristic curve. CRP: C-reactive protein. I-FABP: intestinal fatty-acid binding protein.

CHAPTER 3. AIMS

The aim of this study is to deliver data on diagnostic performance from radiological examinations and blood-based parameters to reduce mortality from AIN, in particular, vascular AIN.

3.1. STUDY 1

To illuminate radiological signs of vascular AIN in unspecific abdominal CT scans compared to similar examinations in acute surgical patients operated on due to a broad range of non-AIN intra-abdominal pathologies.

3.2. STUDY 2

To evaluate the diagnostic performance of D-lactate in AIN patients compared to non-selected patients acutely referred to a department of gastrointestinal surgery due to abdominal pain.

3.3. STUDY 3

To examine the diagnostic performance of I-FABP, endothelin-1 and L-lactate in AIN patients compared to non-AIN patients from the Study 2 cohort.

CHAPTER 4. METHODS

4.1. STUDY 1

4.1.1. STUDY DESIGN

A case–control study was designed to explore radiological findings in the numerous unspecific CT scans performed preoperatively in vascular AIN patients undergoing acute bowel resection compared to a wide variety of other gastrointestinal surgical diseases (169).

4.1.2. PATIENT SELECTION

AIN patients with histologically verified intestinal necrosis (Systematized Nomenclature of Medicine codes: M54000-M54860 & T60000-T69120) or patients with open-close explorative laparotomy or diagnostic laparoscopy (Nordic Medico-Statistical Committee classification of surgical procedure codes: KJAH00 and KJAH01) due to widespread AIN incompatible with life were included from 2006–2009 at The Department of Gastrointestinal Surgery, Aalborg University Hospital, Denmark. Control patients were included during the same period and extracted from the hospital database as the next operated patient. Moreover, only AIN and control patients above 18 years with a CT scan performed within 48 hours before surgery were included. Nonvascular AIN patients were excluded, roughly leaving control patients at a ratio of 1:2 (169).

4.1.3. DATA COLLECTION

An initial CT scan was explored, including phases (noncontrast, arterial-, portovenous phase and combinations) and AIN suspicion status in the referral and radiological report. Additionally, the CT scans were re-evaluated by an experienced gastrointestinal radiologist registering radiological findings in relation to the vasculature, intestine, and extraintestinal findings (169).

The surgical report was reviewed with respect to procedures and pathological findings (169).

4.1.4. ETHICS

The study was approved by The Danish Data Protection Agency under the joint application by The North Denmark Region and by The Scientific Ethical Committee of North Denmark Region (N-20170089), and the study protocol is available at ClinicalTrials.gov (NCT04361110) (169).

4.1.5. STATISTICS

Demographics, findings during surgery, and abdominal phases were reported as numbers and rates or means and 95% confidence intervals. The radiological findings associated with AIN status being binary were modelled and analysed using logistic regression adjusted for age and sex. Adjustment in subgroup analyses was not performed due to low statistical power. Estimates were reported with odds ratios and supplemented with 95% confidence intervals and p-values when reporting adjusted results. P values < 0.05 were considered statistically significant. The analysis was performed using StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC (169).

4.2. STUDIES 2 & 3

4.2.1. STUDY DESIGN

Study two was designed as a cross-sectional case–control study exploring D-lactate elevation as a predictor of AIN case status compared to a large group of non-AIN surgical patients with abdominal pain suffering from a wide variety of surgical diseases. Due to a low number of AIN patients, additional in-hospital high-risk patients suspected to suffer from AIN were included in the study (170).

Study three explored L-lactate, I-FABP or endothelin-1 elevation in relation to AIN case status compared to sex and age balanced non-AIN control patients. AIN and control patients at a ratio of 1:5 were included from the general surgical cohort from Study 2 (171).

4.2.2. PATIENT SELECTION

Every adult patient above 18 years of age referred to The Department of Gastrointestinal Surgery, Aalborg University Hospital, Denmark, due to abdominal pain from January 6, 2015, to June 9, 2016, was consecutively included in the study. A blood sample was drawn after written and verbal consent just after hospital contact. An additional inclusion was performed within in-hospital patients suspected to suffer from AIN. They were included after written and verbal consent at the time for decision-making for acute surgery. Surgical verification of acute intestinal necrosis or ischaemia was retrospectively registered from the surgical report. Control patients were defined as non-AIN patients in the same cohort (170,171).

4.2.3. DATA COLLECTION

Comorbidity, earlier surgery, medication, intraoperative findings, surgical procedures, and AIN case status were registered from the hospital database (170,171).

4.2.4. PREPARATION AND ANALYSIS OF BLOOD SAMPLES

Preanalytical handling for the blood samples included centrifugation and storage at -80 °C. Detailed preanalytical stability tests mimicking actual routines for research samples in the busy emergency department were performed for alpha glutathione transferase, ischaemia modified albumin, glucose transporter-5 (Glut-5), spermin synthase and fatty acid transport protein-4 (FATP-4) as well as D-lactate, L-lactate, I-FABP, and endothelin-1. The latter four samples passed the stability tests and were selected for further analysis. Great expectations have been placed on D-lactate as an AIN biomarker. Thus, considerable effort was spent on the operationalization of D-lactate analysis in a fully automated spectrophotometric setup (172). The analysis was performed according to Rasmussen et al. (172). Initial analytical considerations were built on cut-off levels in the literature as mentioned. Due to a much lower cut-off in our data considerable analytical noise due to lipemic interference was encountered, excluding roughly half of the AIN and control patients from the analysis (170).

Venous L-lactate was analysed in a routine setup in a hospital laboratory. I-FABP and endothelin-1 were analysed using commercially available ELISA-kits (171).

4.2.5. ETHICS

Studies two and three were approved by The Scientific Ethical Committee of North Denmark Region (N-20170089) and the protocol was made publicly available at ClinicalTrials.gov (NCT05665946). Included patients were enrolled in the study after verbal and written content (170,171).

4.2.6. STATISTICS

Tabulation of categorical variables was reported with absolute numbers and fractions. Continuous variables were reported as the means and standard deviations due to normality. However, in study three, the “Hours between blood sample and surgery”-variable was reported as the median and interquartile range due to right skewness. Additionally, differences in categorical variables between AIN and control patients were tabulated with risk differences and 95% confidence intervals. Differences in means for continuous variables are shown with standard deviation (170,171).

The fraction of patients with D-lactate below the limit of quantification was tabulated, ensuring a valid impression of the reported mean D-lactate concentrations (170).

Diagnostic performance was deliberated from the receiver operator characteristic (ROC) curves and tabulated as the area under the curve (AUC) with a 95% confidence interval. Each cut-off value was computed using Youden index estimation. Sensitivity and specificity were calculated according to the corresponding cut-off values. The calculation of AUC of the combined I-FABP + endothelin-1 used leave-one-out cross

validation adjusting for inflated AUC values. P values < 0.05 were considered statistically significant. The analysis was performed using StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC. (170,171).

CHAPTER 5. RESULTS

5.1. STUDY 1

5.1.1. STUDY POPULATION

- In total, 427 procedures with a histological diagnosis of intestinal necrosis were identified (169).
- Additionally, 25 exploratory laparotomies with widespread intestinal necrosis incompatible with life were identified (169).
- Forty-eight AIN patients suffering from vascular AIN with abdominal CT scans within 48 hours preoperatively were ultimately included (169).
- Eighty control patients fulfilled the inclusion criteria (169).
- Baseline demographics are displayed in Table 5-1 (169).
- AIN patients were significantly older than control patients (169).
- Surgical findings during surgery are displayed in Paper 1 (Appendix I) (169).

Table 5-1: Demographic variables in 128 patients. Reproduced with permission from Springer Nature (169).

Variable	Controls N(%)	Patients with intestinal ischaemia N(%)	OR(95% CI)	P-value
Total number of patients	80 (100.0)	48 (100.0)		
Female gender	40 (50.0)	32 (66.7)	2.00 (0.95;4.20)	0.068
Male gender	40 (50.0)	16 (33.3)	0.50 (0.24;1.05)	0.068
Age >= 70 years	30 (37.5)	32 (66.7)	3.33 (1.57;7.07)	0.002
Age <70 years	50 (62.5)	16 (33.3)	0.30 (0.14;0.64)	0.002
Age (mean(years)) (SD)	62.9 (16.6)	70.8 (13.0)		

OR: Odds ratio. Values in parentheses (95% CI) are 95% confidence intervals.

5.1.2. IMAGING PHASES

- Abdominal CT scanning phases were equally distributed between AIN and control patients and are tabulated below in Table 5-2 (169).
- One out of five patients were offered a noncontrast CT scan (169).
- Arterial phase abdominal CT scans were rarely performed. Even in combination with other phases and with AIN suspicion mentioned in the referral (169).

Table 5-2: Abdominal CT scan phases in 128 patients. Reproduced with permission from Springer Nature. (169)

Variable	*Controls* N(%)	*AIN patients* N(%)
Noncontrast CT only	18 (22.5)	11 (22.9)
Contrast-enhanced CT	62 (77.5)	37 (77.1)
AP only	6 (7.5)	4 (8.3)
AP + PV	0 (0.0)	3 (6.3)
PV only	53 (66.3)	29 (60.4)
PV + NC	2 (2.5)	1 (2.1)
AP + PV + NC	1 (1.3)	0 (0.0)

AP: Arterial phase. PV: Porto-venous phase. NC: Noncontrast phase.

5.1.3. CLINICAL AND RADIOLOGICAL SUSPICION OF AIN

- In the initial radiological report, one out of three AIN patients and one out of five control patients were suspected to suffer from AIN (169).
- One out of five radiological referrals in AIN patients included a specific suspicion of AIN (169).

5.1.4. RADIOLOGICAL FINDINGS

- The three main groups of radiological findings, intestinal wall pathology, gastrointestinal vessel pathology, and intestinal diameter, were independent predictors of AIN (Table 5-3) (169).
- The unadjusted subgroup analysis of radiological findings implied that pneumatosis intestinalis (Figure 2-1), increased contrast enhancement in the bowel wall (Figure 2-3), inferior mesenteric artery arteriosclerosis, and colon contraction (Figure 2-2) were predictors of AIN (169).

Table 5-3: Regression estimates on CT-findings in 128 patients with crude estimates on subgroups. Reproduced with permission from Springer Nature (169).

	Controls N(%)	AIN Patients N(%)	Crude OR (95% CI)	Adjusted* OR (95% CI)	P value
Male gender			0.50 (0.24;1.05)	0.41 (0.14;1.17)	
Age <70 years			0.30 (0.14;0.64)	0.97 (0.30;3.15)	
Intestinal wall pathology	23 (28.7)	33 (68.8)	5.5 (2.5;11.9)	7.4 (2.3;24.0)	<0.001
Abnormal CE in bowel wall	3 (3.8)	7 (14.6)	4.4 (1.1;17.9)		
Hyperdense bowel wall	5 (6.3)	6 (12.5)	2.1 (0.6;7.4)		
Increased CE in bowel wall	2 (2.5)	11 (22.9)	11.6 (2.4;55.0)		
Pneumatosis intestinalis	3 (3.8)	19 (39.6)	16.8 (4.6;61.1)		
Thickened bowel wall	21 (26.3)	24 (50.0)	2.8 (1.3;6.0)		
GI vessel pathology	32 (40.0)	43 (89.6)	12.9 (4.6;36.1)	19.3 (4.6;80.5)	<0.001
Coeliac trunk occluded	0 (0.0)	1 (2.1)	1.0 (.)		
SMA occlusion	2 (2.5)	5 (10.4)	4.5 (0.8;24.4)		
IMA occlusion	0 (0.0)	3 (6.3)	1.0 (.)		
Coeliac trunk arteriosclerosis	25 (31.3)	30 (62.5)	3.7 (1.7;7.8)		
SMA arteriosclerosis	25 (31.3)	35 (72.9)	5.9 (2.7;13.1)		
IMA arteriosclerosis	10 (12.5)	36 (75.0)	21.0 (8.3;53.3)		
Mesenteric venous occlusion	2 (2.5)	1 (2.1)	0.8 (0.1;9.4)		
Portal venous gas	0 (0.0)	3 (6.3)	1.0 (.)		
Solid organ infarction	0 (0.0)	1 (2.1)	1.0 (.; .)		
Ekstraintestinal pathology	53 (66.3)	33 (68.8)	1.1 (0.5;2.4)	0.4 (0.1;1.4)	0.148
Ascites	48 (60.0)	27 (57.4)	0.9 (0.4;1.9)		
Pneumoperitoneum	27 (33.8)	11 (22.9)	0.6 (0.3;1.3)		
Stranding	15 (18.8)	23 (47.9)	4.0 (1.8;8.8)		
Intestinal diameter	33 (41.3)	37 (77.1)	4.8 (2.1;10.7)	4.7 (1.6;13.4)	0.004
Colon contraction	6 (7.5)	21 (43.8)	9.6 (3.5;26.3)		
Colon dillatation	3 (3.8)	7 (14.6)	4.4 (1.1;17.9)		
Small bowel contraction	14 (17.5)	7 (14.6)	0.8 (0.3;2.2)		
Small bowel dillatation	26 (32.5)	24 (50.0)	2.1 (1.0;4.3)		

*OR: odds ratio. Values in parentheses (95% CI) are 95% confidence intervals. *:Adjustment for all main radiological categories, age and gender. CE: contrast enhancement. GI: Gatrointestinal. SMA: Superior mesenteric artery. IMA: Inferior mesenteric artery.*

5.2. STUDY 2

5.2.1. STUDY POPULATION

- In total, 2871 acutely referred patients were included consecutively, and 87 acute in-hospital patients suspected to suffer from AIN were subsequently included in the study (170).

- Forty-four AIN patients and 2914 control patients were included in the analysis (170).
- AIN patients were significantly older than control patients, and 3-month mortality was considerably higher in AIN patients than in control patients (170).
- After analysis, and due to lipemic interference, 23 AIN patients (52%) and 1456 control patients (49%) were evaluated (170).
- No differences in characteristics were found between the analysed and excluded patient groups (170).
- Every AIN patient used medicine compared to three out of four control patients (170).
- Two out of three AIN patients used anticoagulation medicine compared to one out of four control patients (170).
- Baseline demographics are displayed in Table 5-4 (170).
- Additional surgical procedures and final diagnoses are to be presented in Paper 2 (Appendix II) (170).

Table 5-4: Characteristics of 1479 acute surgical patients with D-lactate estimation. Reproduced with permission from Elsevier Ltd. (170).

Variable	Controls N (%)	AIN patients N (%)	Risk diff. (% (95% CI))	P value
Patients	1456 (100.0)	23 (100.0)		
Male	659 (45.3)	9 (39.1)	-6.1 (-26.2; 14.0)	0.550
Age above 70 years	493 (33.9)	16 (69.6)	35.7 (16.7; 54.7)	0.000
Tree month mortality	113 (7.8)	7 (30.4)	22.7 (3.8; 41.5)	0.018
Age (mean(years))(SD)	57.0 (21.2)	75.4 (10.5)	18.4 (14.0; 22.7)	0.000
Diabetes mellitus	152 (10.4)	3 (13.0)	2.6 (-11.3; 16.5)	0.713
Insulin dependent DM	51 (3.5)	0 (0.0)	-3.5 (-4.4; -2.6)	0.000
Hypertension	446 (30.6)	13 (56.5)	25.9 (5.5; 46.3)	0.013
Heart disease	303 (20.8)	8 (34.8)	14.0 (-5.6; 33.6)	0.162
Arteriosclerotic disease	312 (21.4)	10 (43.5)	22.0 (1.7; 42.4)	0.034
Cancer	255 (17.5)	2 (8.7)	-8.8 (-20.5; 2.9)	0.139
GI-cancer	29 (2.0)	0 (0.0)	-2.0 (-2.7; -1.3)	0.000
EA operations	689 (47.3)	11 (47.8)	0.5 (-20.1; 21.1)	0.962
Active smoking	325 (22.3)	5 (21.7)	-0.6 (-17.6; 16.4)	0.946
Use of medication	1100 (75.5)	23 (100.0)	24.5 (22.2; 26.7)	0.000
Use of anticoagulants	406 (27.9)	15 (65.2)	37.3 (17.7; 56.9)	0.000

SD: Standard deviation. DM: Diabetes mellitus. GI: gastrointestinal. EA: earlier abdominal. Risk diff.: Risk difference. Values in parentheses (95% CI) are 95% confidence intervals. Difference for categorical variables is difference in proportion (risk difference) and for continuous variables difference in mean.

5.2.2. LIPEMIC INTERFERENCE

- The study cut-off for D-lactate of 0.0925 mM is clearly lower than the average D-lactate cut-off stated in the literature (170). Most of the studies performed on D-lactate in AIN patients reported cut-offs > 0.2 mM (125,129,142), whereas Nuzzo et al. reported a considerably lower cut-off (137).
- The low cut-off resulted in considerable noise from lipemic interference. Elimination of false high D-lactate measurements due to lipemic interference caused exclusion of 1458 control patients and 21 AIN patients for the final analysis (170).
- A large proportion of participants demonstrated D-lactate below the limit of quantification. Additionally, a pronounced right-skewed D-lactate distribution in both AIN and control patients was demonstrated (Figure 5-1) (170).

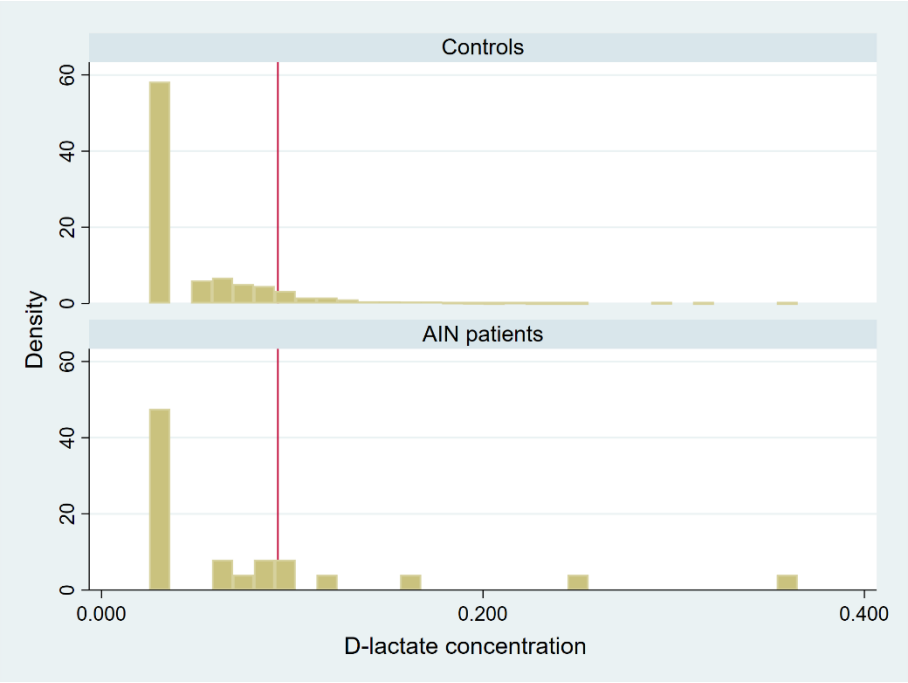

Figure 5-1: D-lactate concentrations in 23 AIN patients and 1456 controls . Red line: D-lactate cut-off. D-lactate concentration in mM. (Reproduced with permission from Elsevier Ltd.) (170).

- A large relative fraction of test results was below the limit of quantification in AIN patients (52%) and control patients (55%) (170).

5.2.3. DIAGNOSTIC PERFORMANCE FOR D-LACTATE

- The mean D-lactate level in AIN patients was not significantly different from that among control patients (170).
- The AUC and sensitivity for D-lactate with respect to AIN were low and are displayed in Table 5-5 (170).
- Specificity for D-lactate discriminating AIN from control patients was acceptably high (170).
- Subgroup analysis, particularly references to elderly patients, high-risk, and low-risk patients, is roughly identical to the one reported for the group (170).

Table 5-5: Diagnostic performance for D-lactate. Main results and subgroups. Reproduced wth permission from Elsevier Ltd. (170).

	AIN (N)	Controls (N)	AUC (95% CI)	Sens.	Spec.	PPV*	NPV*
Main results	44	2914	0.50 (0.40;0.60)	0.270	0.830	0.020	0.990
Patients above 70 years	28	913	0.44 (0.31;0.57)	0.250	0.780	0.030	0.970
High-risk only	27	65	0.53 (0.40;0.66)	0.330	0.780	0.390	0.740
Low-risk only	17	2849	0.40 (0.25;0.55)	0.180	0.830	0.010	0.990

*AUC: Area under the receiver operator characteristic curve. Values in parentheses (95% CI) are 95% confidence intervals. Sens.: Sensitivity. Spec.: Specificity. PPV: Positive predictive value. NPV: Negative predictive value. Cut-off value was estimated to 0.0925 mM corresponding to a Youden index of 0.198 (SE: 0.105) based on the complete cohort. *Prevalence of AIN in data might be overestimated due to inclusion of high-risk patients hence PPV and NPV should be assessed with caution.*

5.3. STUDY 3

5.3.1. STUDY POPULATION

- The 44 AIN patients from study two and an age and sex balanced subgroup of the control patients in the 1:5 ratio from the same cohort constituted the study population (171).
- Baseline demographics are displayed in Table 5-6 (171).
- Only three-month mortality and use of anticoagulation were significantly higher in AIN patients than in control patients Table 5-6 (171).
- Surgical procedures are tabulated in Paper 3 (Appendix III) (171).

Table 5-6: Characteristics of 268 acute surgical patients. Reproduced with permission from Taylor & Francis (171).

Variable	Controls N=225 N (%)	AIN patients N=43 N (%)	Difference (% (95% CI))	P value
High-risk patients	8 (3.6)	27 (62.8)		
Male	94 (41.8)	19 (44.2)	2.4 (-13.8; 18.6)	0.771
Age above 70 years	132 (58.7)	28 (65.1)	6.4 (-9.2; 22.1)	0.420
Three-month mortality	25 (11.1)	13 (30.2)	19.1 (4.8; 33.5)	0.009
Age. years*	72.6 (13.5)	73.3 (13.6)	0.8 (-3.6; 5.1)	0.738
Diabetes mellitus	36 (16.0)	7 (16.3)	0.3 (-11.8; 12.3)	0.964
Insulin-dependent DM	13 (5.8)	3 (7.0)	1.2 (-7.0; 9.4)	0.775
Hypertension	99 (44.0)	25 (58.1)	14.1 (-2.0; 30.3)	0.086
Heart disease	85 (37.8)	14 (32.6)	-5.2 (-20.6; 10.2)	0.507
Arteriosclerotic disease	97 (43.1)	19 (44.2)	1.1 (-15.1; 17.3)	0.897
Cancer	4 (1.8)	1 (2.3)	0.5 (-4.3; 5.4)	0.824
GI-cancer	3 (1.3)	0 (0.0)	-1.3 (-2.8; 0.2)	0.082
EA operations	117 (52.0)	23 (53.5)	1.5 (-14.8; 17.8)	0.858
Active smoking	47 (20.9)	10 (23.3)	2.4 (-11.4; 16.1)	0.735
Use of medication	202 (89.8)	41 (95.3)	5.6 (-1.9; 13.0)	0.143
Use of anticoagulants	107 (47.6)	28 (66.7)	19.1 (3.4; 34.8)	0.017

**mean (SD). SD: Standard deviation. DM: Diabetes mellitus. GI: Gastrointestinal. EA: earlier abdominal. Values in parentheses (95% CI) are 95% confidence intervals. Difference for categorical variables is difference in proportions (risk difference); for continuous variables it is difference in means.*

5.3.2. DIAGNOSTIC PERFORMANCE FOR L-LACTATE, I-FABP AND ENDOTHELIN-1

- Diagnostic performances for L-lactate, I-FABP, and endothelin-1 are displayed in Table 5-7 (171).
- I-FABP and endothelin-1 combined were cross-validated, showing an AUC, sensitivity, and specificity similar to endothelin-1 alone and are displayed in Table 5-7 (171).
- Diagnostic performance for L-lactate, I-FABP, and endothelin-1 in subgroups are displayed in Table 5-8 (171).

Table 5-7: Diagnostic performance for L-lactate, I-FABP and endothelin-1 in 43 AIN patients and 225 control patients. Reproduced with permission from Taylor & Francis (171).

	Cut-off	AUC (95% CI)	Sens.	Spec.
L-Lactate	0.72	0.61 (0.52; 0.69)	0.84	0.36
I-FABP	3045	0.71 (0.62; 0.81)	0.63	0.77
Endothelin-1	3.31	0.74 (0.67; 0.82)	0.81	0.64
I-FABP + Endothelin-1*	(.)	0.74 (0.66; 0.82)	0.79	0.62

*Cut-off value in mM. AUC: area under the receiver operator characteristic curve. CI: confidence interval. Sens.: Sensitivity. Spec.: Specificity. The sensitivity and specificity are relative to the cut off corresponding to the Youden index for L-lactate, I-FABP, endothelin-1 and the combination of I-FABP and endothelin-1. *Optimism-corrected.*

Table 5-8: Diagnostic performance for L-lactate, I-FABP and endothelin-1 in subgroups compared to 225 control patients. Reproduced with permission from Taylor & Francis (171).

	Cut-off	AUC (95% CI)	Sens.	Spec.
High-risk patients (N=27)				
L-Lactate	0.86	0.64 (0.54; 0.75)	0.74	0.52
I-FABP	3045	0.71 (0.58; 0.84)	0.67	0.77
Endothelin-1	3.34	0.76 (0.67; 0.85)	0.81	0.65
I-FABP + Endothelin-1*	(.)	0.74 (0.63; 0.86)	0.67	0.80
Nonhigh-risk patients (N=16)				
L-Lactate	0.66	0.54 (0.40; 0.68)	0.94	0.29
I-FABP	3408	0.72 (0.59; 0.84)	0.56	0.82
Endothelin-1	3.31	0.72 (0.62; 0.82)	0.81	0.64
I-FABP + Endothelin-1*	(.)	0.74 (0.64; 0.84)	0.88	0.57
Vascular AIN patients (N=10)				
L-Lactate	0.73	0.68 (0.52; 0.84)	1.00	0.38
I-FABP	3230.50	0.70 (0.46; 0.94)	0.70	0.80
Endothelin-1	3.34	0.78 (0.68; 0.88)	0.90	0.65
I-FABP + Endothelin-1*	(.)	0.74 (0.55; 0.94)	0.70	0.80

*AIN: Acute intestinal necrosis. Sens.: Sensitivity. Spec.: Specificity. Cut-off value in mM. AUC: area under the receiver operator characteristic curve. CI: confidence interval. The sensitivity and specificity are relative to the cut off corresponding to the Youden index for L-lactate, I-FABP, endothelin-1 and the combination of I-FABP + endothelin-1. *Optimism-corrected.*

CHAPTER 6. DISCUSSION

AIN is a highly fatal disease. Mortality rates remain above 50% despite powerful diagnostic tolls used and sufficient progress in all facets of the medical field. Violation to the timeframe of approximately 6 hours before irreversible changes in the intestine from a vascular obstructive event emerge appears to be the main cause of the high mortality. The vital suspicion of AIN is impeded by the absence of reliable clinical or standard biochemical signs. Namely, vascular AIN is highly insidious in the early phase of the disease. Thus, relevant treatment should not be immediately initiated.

If diagnosis and treatment are to be initiated within six hours from a vascular event, potentially before AIN suspicion is raised, an early and reliable biomarker and urgent abdominal CT scan are warranted.

Research in this initial six-hour timeframe is scarce and seems almost impossible to perform. A major portion of the literature is exclusively in patients where the suspicion of AIN is raised (12,28–33,68,77,173,174). Thus, the design of these studies excludes a portion of the relevant patient group. This implies a nonnegligible selection bias in the literature concerning AIN. Additionally, this forcefully questions at least the transferability of a major portion of the research findings to routine clinical procedures, namely, to very early patient evaluation, and might explain the roughly unchanged mortality rate in recent decades.

A minor fraction of the literature concerns the evaluation of patients immediately after hospital contact. Sala et al. conducted a randomized controlled trial by performing abdominal CT within the first hour of admission in a general surgical population (175). They reported that “CT imaging often revealed diagnoses that were unexpected, and sometimes unrelated to the initial presentation” in 20% of the “one-hour-abdominal-CT-scan” portion of the patients (175). This might also affect AIN patients, although they were not reported. Nevertheless, the authors failed to show a considerable impact on hospital stay or mortality from the one-hour abdominal CT scan.

Very early patient evaluation and diagnosis might be the Holy Grail for better prognosis of AIN patients and is the aim of this study.

6.1. RADIOLOGY

Abdominal CT scans in AIN patients have been thoroughly researched. Sensitivity or specificity (29,76,176) or even both (30,31,53,68) reached almost 1.00 in several studies. Additionally, the availability and frequency of CT scans performed in the acute setting is under intense increase. Patients with unexplained abdominal pain and advanced age are commonly scanned after fast-track protocols around the clock (177).

Diagnostic certainty in patients with abdominal pain is secured by early abdominal CT scan within 1 hour from admission, and AIN patients might benefit from this approach (175). Given this powerful and accessible diagnostic tool in the clinic, why does the mortality remain above 50%?

Several challenges arising in the clinic counteract the transferability of the impressive research results mentioned. First, patients in the early course of AIN frequently lack objective findings, particularly peritoneal reaction (20,44,178), violating the initial suspicion of the first examination. Second, if the AIN suspicion is not mentioned in the radiological referral, the radiologist is less prone to revise the scan with respect to AIN (20). Third, a considerable portion of patients with advanced age suffer from nephropathy to some extent, especially in the acute setting with fasting, nausea and vomiting, causing a widespread tendency to omit intravenous contrast, compromising scanning quality (43). Fourth, although the literature uncovers clear radiological signs of AIN, so-called "specific" signs, the retrospective literature shows conflicting evidence of the sensitivity and specificity rates in the clinic (Table 2-1). Thus, the clinical implication of these specific signs of AIN is impaired (53). Fifth, AIN is a relatively rare disease, and the low number of AIN patients in the clinic (23) opposes the ubiquitous suspicion.

These clinical obstacles inspired us to conduct the first study. For several reasons, we performed a retrospective study in all vascular AIN patients in the exact period with a specimen showing intestinal necrosis or with open-close surgery due to widespread AIN incompatible with life. In this way, each AIN patient with an abdominal CT within 48 hours preoperatively was included. Additionally, with revision of all preoperative CT scans, we could reveal every radiological sign in abdominal CT scans, both specific AIN signs and nonspecific signs of pathology, potentially uncovering early signs of AIN. Moreover, we illuminated the lack of suspicion of AIN in acute patients in the daily clinic.

6.1.1. THE INITIAL CLINICAL AIN SUSPICION AND THE FOLLOWING RADIOLOGICAL REPORT

Our study underlines the problem with an absent clinical suspicion of AIN. AIN suspicion was mentioned in only 1 out of 5 radiological referrals in AIN patients in our study. Lehtimäki et al. found in their study 1 out of 3 radiological referrals with AIN suspicion (20). Additionally, only one out of three radiological reports in AIN patients includes AIN suspicion, whereas one out of five control patients is suspected to suffer from AIN. Lehtimäki found that 14% of AIN radiological reports were incorrect, which is much lower than that found in our study and might be explained by the way radiological reports were evaluated by Lehtimäki et al. They evaluated the radiological report as correct if AIN suspicion/diagnosis was stated or a correct vascular description with emboli was asserted. In our study, we evaluated the report as correct only if the AIN diagnosis was suspected and mentioned. Additionally, one

could speculate that research in AIN in the actual radiological department, as in the department of Lehtimäki, might increase the correctness of vascular description. Moreover, this might unveil the power of education and information about AIN in a certain department.

6.1.2. NONCONTRAST PHASES ALONE

As mentioned, intravenous contrast is frequently omitted in acute patients due to relatively impaired renal function on fragile evidence (43–46). In our study, we found that the noncontrast CT scan rate (one out of five patients with noncontrast CT scans alone) was slightly higher than that in the studies by Mazzei et al. (47) and Verdot et al. (48). These newer studies might uncover a recent tendency to administer contrast in acute patients despite renal impairment or a shift towards a lower glomerular filtration rate limit before contrast administration according to recent guidelines (179).

6.1.3. SPECIFIC RADIOLOGICAL AIN FINDINGS

Kärkkäinen et al. (68) defined specific AIN findings as SMA embolus, SMA thrombosis, mesenteric venous thrombosis, intestinal pneumatosis, portal venous gas and unenhanced or poorly enhanced bowel wall segments. Roughly every second AIN patient in our study showed no specific radiologically AIN signs. Additionally, one out of 10 non-AIN control patients experienced these findings. Intestinal pneumatosis, SMA occlusion, mesenteric venous thrombosis, and poorly enhanced bowel wall were present in both healthy and in other control patients, showing the difficulties in adapting these radiological signs as specific findings in AIN patients.

One of the most prominent specific radiological signs of AIN from the literature, portal venous gas (30,53,55,76), was infrequent in this study. This might underline the mentioned selection bias in the literature, the high proportion of late AIN in the literature, or that a major portion of our included AIN patients are early in the AIN course. However, the latter statement is questionable because every included patient in our study experienced histological intestinal necrosis or widespread AIN incompatible with life.

6.1.4. WHERE TO GO? – EARLY RADIOLOGICAL SIGNS!

Reducing mortality by earlier diagnosis and treatment brings early radiological signs to the forefront. Early radiological signs include splanchnic vessel pathology (thromboembolic occlusion, filling defects and mesenteric vein thrombosis), bowel wall pathology (bowel-wall thickening, hypoattenuation, hyperattenuation, absent wall enhancement and bowel wall halo-sign), and intestinal contraction (Table 2-1).

In contrast to a major portion of AIN research, which only includes patients where AIN is suspected (27–33), we included suspected (potentially late AIN) and

nonsuspected AIN patients (potentially early AIN). In this way, we try to avoid the potential selection bias that is afflicting the mentioned literature. Nevertheless, the small sample size weakened our conclusions. This prevented a detailed adjustment in the statistical analysis, uncovering the importance of every single finding and forcing us to reveal the significance of groups of findings. Nevertheless, our findings with respect to splanchnic vessel pathology, intestinal wall pathology, and intestinal diameter as independent predictors closely follow the abovementioned early sign categories.

Splanchnic vessel findings were identified in this study, although they were relative rare. We found SMA occlusion as the most frequent early radiological sign of vessel pathology. Bowel wall findings were more frequent. Bowel wall thickening was the most frequent sign in our study, but hyperattenuation was also pronounced. Overall, several early signs are present in this study, meeting our research goals by unveiling early radiological signs even in CT scans nonspecifically targeting a suspected AIN. This finding underlines the unused potential of radiologic examination in this study-population. Thus, early findings must alert radiologists and surgeons even if the AIN diagnosis is not suspected. This action might accelerate the diagnostic process and ultimately reduce mortality. Finally, a few radiological findings must be addressed.

6.1.4.1. Intestinal contraction

Interestingly, we discovered at least one sign potentially not mentioned in the literature–contraction of the (left) colon. Contracted intestine appears to constitute three different pathophysiologic conditions in the literature. First, the contraction of the AIN injured segment (78,180,181). Second, spastic reflex ileus does not necessarily affect the injured segment alone but also the non-AIN-affected intestine, followed by dilatation of the intestine with intramural and mesenteric oedema (180). We suggest a third form, a spastic reflex contraction of the (left) colon without radiological wall changes. The latter is, to our knowledge, not mentioned in the literature. One might speculate that it follows ischaemia of the colon, but roughly half of the AIN patients with this contraction have a viable colon. A possible explanation might be similar to the mentioned reflex ileus with the primary effect of the left colon or an energy-saving reaction in the colon transferring blood to the injured segment(s). Thus, it remains unclear whether it is a new finding, a part of spastic reflex ileus, or a chance finding. If this is a result of a neurogenic reflex, it might be an early radiological sign, but the timely relation is not illuminated in this study.

6.1.4.2. Arteriosclerosis

Arteriosclerosis is frequent in advanced age (182), which is in accordance with our findings identifying this in the control group as well. Nevertheless, the rate of arteriosclerosis in AIN patients compared to control patients is doubled in SMA and immoderately increased in IMA. It is well known (182) that patients suffering from arteriosclerosis are prone to thromboembolic events, and this statement is supported by the generalized arteriosclerosis in the AIN group. Arteriosclerosis in the IMA is

not a specific sign of AIN nor an early sign of AIN, in a classical meaning. Nevertheless, it is registered early due to its chronic nature. Arteriosclerosis in the IMA was reported in three out of four AIN patients in our study.

6.2. BLOOD-BASED PARAMETERS

The ultimate AIN biomarker has been looked for over decades. Standard blood-based parameters have failed to show sufficient diagnostic performance in AIN diagnosis (Table 2-2). Additionally, many proposed novel biomarkers have never reached a clinical setting. Nevertheless, thorough and promising experimental (132), human studies (108), and reviews (141) on D-lactate prompted us to initiate the second study. The need for a final conclusion on D-lactate with respect to AIN patients in a general surgical population and the implication of the analysis in a large, automated setup gave rise to a large-scale study including adult patients who were referred to a single gastrointestinal surgical department with abdominal pain. This ensured the inclusion of unsuspected AIN patients with a blurred clinical and biochemical picture. Additionally, inclusion before clinical evaluation spared time-consuming clinical and paraclinical considerations, making early biochemical signs available.

A considerable effort was spent in the development of the D-lactate analysis, making it operational on an automated analytical setup ensuring fast and reliable analysis reports around the clock (172). Nevertheless, half of the patient cohort in this study was excluded from the analysis due to lipemic interference, and D-lactate failed to distinguish AIN patients from non-AIN patients in the nonexcluded part of the patients. As mentioned, this finding was in accordance with some newer studies (125,137,142).

The cut-off in this study was in the range of the literature (0.012-0.38 mM (125,129,137,142)), although most of the studies found cut-offs above 0.2 mM, twice as high as the reported cut-off in our study. Similarly, the AUC of D-lactate in diagnosing AIN has been reported in several studies (AUC: 0.44–0.69 (125,128,130)). The AUC of our study is within this range. Moreover, the pooled sensitivity of D-lactate was reported in a meta-analysis based on six heterogeneous studies in AIN patients of 0.72 (0.59;0.83) and a pooled specificity of 0.74 (0.69;0.79) (141). Nuzzo et al. reported a sensitivity of 0.98 and specificity of 0.17 in a recent study (137). The sensitivity of our study is lower than these values, but the specificity is higher. We calculated the cut-off according to the Youden index. If the cut-off was changed within the range from the literature, sensitivity and specificity would be affected accordingly. Improving the sensitivity would be at the cost of the sensitivity and vice versa. Thus, our cut-off is low in the reported range in the literature, which also affects the sensitivity and specificity. Nevertheless, the AUC is also low, leading to the final conclusion. Nuzzo et al. reported the lowest cut-off and argued that the homogenous patient cohort in their study excluding patients such as NOMI patients and left colon AIN explains the difference in diagnostic performance compared to the literature.

Nevertheless, their conclusion about the inability of D-lactate to discriminate AIN patients from control patients is in accordance with the conclusion in our study.

6.2.1. LIPEMIC INTERFERENCE

Despite comprehensive efforts to automate and validate D-lactate in a large, automated setup, non-negligible lipemic interference was observed (170). Therefore, the analysis of D-lactate in half of the patients in this study was violated due to a low cut-off.

Lipemic interference in the spectrophotometric setup is caused by absorption of the light by lipid particles, compromising the analysis results (183). Lipemic interference is only very sparsely addressed in the AIN literature. Nielsen et al. reported no significant interference in their experimental study (184). Whether this is related to the cut-off of 0.2 mM or transferability issues from animal to human studies is unclear. In regard to human studies, lipemic interference is, to our knowledge, not addressed in detail thus far. Nuzzo et al. reported a much lower cut-off (0.012 mM D-lactate) compared to our study using the same spectrophotometric setup on a Cobas analyser (Roche) (137). Indeed, automated analysers report turbidity in a formalized way, making lipemic interference clear (183). If the lipemic interference is in relation to a low cut-off, it might be considerable in the study from France, but it is not reported (137).

The exclusion of half of the study population due to lipemic interference appears to be independent of the final diagnosis of the patients, including AIN. The range of different diseases was roughly the same in the included and excluded patients, as shown in Paper 2 (Appendix II) (170). Similarly, the rate of excluded patients was roughly the same in AIN patients and the control group (170).

6.2.2. TEST RESULTS BELOW THE LIMIT OF QUANTIFICATION

A considerable proportion of the D-lactate test results were below the limit of quantification. Only Nuzzo et al. reported median D-lactate values in AIN and control patients below the cut-off in our study (137). They did not comment on the limit of quantification. Whether this was due to their use of another D-lactate analyser kit (Biosentec D-lactic acid kit) is unclear.

To our knowledge, this issue is not addressed in the D-lactate literature, probably due to the higher D-lactate values reported and the nonautomated analytical methods used in smaller studies.

6.2.3. STABILITY TEST

Blood samples from almost 3000 patients were collected after verbal and written consent at the same time as the routine blood samples and just after hospital contact (170). Preanalytical handling included centrifugation and storage at -80 °C. Stability tests were performed in healthy control patients (blood donors) addressing the variation in workload in daily clinical practice and the potential suboptimal handling of the samples at busy moments before the samples were stored. The timespan of up to a weekend before storage of the collected tubes was modelled in the stability test setup, unveiling the impact of this potential timespan. All the blood-based biomarkers reported in this study passed these preanalytical tests.

6.2.4. NOVEL BIOMARKERS

Settling the discussion of D-lactate, we researched other novel biomarkers, preferring the most promising from the literature. Alpha glutathione transferase and ischaemia modified albumin revealed low values around or under the detection limit in the stability test. Glut-5, spermin synthase and FATP-4 were significantly elevated in the stability tests after a workday (7 hours) before centrifugation, thus failing the stability test. In other words, alpha glutathione transferase, ischaemia modified albumin, Glut-5, spermin synthase and FATP-4 failed the stability test in healthy control patients and were abandoned. However, these biomarkers might be of value in other settings. L-lactate, I-FABP, and endothelin-1 passed the stability tests and were further evaluated in Study 3.

6.2.5. L-LACTATE

L-lactate as an AIN biomarker was explored in Study 3 in a case–control study and analysed in an automated setup in a routine laboratory (171). With a low specificity and AUC, L-lactate failed to discriminate between AIN and control patients. L-lactate is a metabolic marker (95) and may better discriminate in another control group. We addressed the selection of control patients at a AIN patients to control ratio of 1:5 and balanced age and sex from the Study 2 cohort. This ensured a relevant control group including patients mirroring AIN-like symptoms and comorbidity. Table 5-4 shows a satisfying distribution of comorbidities (including AIN predisposition factors such as cardiac disease, diabetes, and arteriosclerotic disease), earlier abdominal surgery, smoking habits and medication except the use of anticoagulants (171). Moreover, subgroup analysis did not change the conclusion (Table 5-5). As mentioned, the research on L-lactate with respect to AIN is conflicting. Brillantino et al. concluded that L-lactate showed good diagnostic accuracy in vascular AIN and NOMI patients (102). Nevertheless, they included suspected AIN patients alone and excluded a wide range of patients, including patients experiencing renal failure, shock, sepsis, and diabetes during metformin treatment. The excluded patients in the study were among others AIN-like patient cases and might explain their positive conclusion on L-lactate

compared to our study. Additionally, Brillantino et al. confirmed the AIN diagnosis by radiology alone in some patients, showing a different AIN definition compared to surgically verified AIN in our study. Matsumoto et al. reported significant L-lactate elevation in NOMI patients (104). Our study included a wide range of AIN patients, which might explain our different conclusion from Matsumoto et al.

6.2.6. I-FABP

The small enterocyte protein I-FABP was also explored in Study 3. The specificity and AUC in our study almost reached the confidence intervals of the meta-analysis by Sun et al. (151). The sensitivity in our study remains lower than the sensitivity reported by Sun et al. In their meta-analysis, heterogeneity was considerable, and the 9 included studies with small sample sizes, different cut-offs in relation to the single kit (type-name not reported in all studies) and different reference standards violated their conclusions. Nevertheless, the sensitivity reported in our study is within the confidence intervals of seven out of nine studies from the meta-analysis. Similarly, the specificity of our study is inside the confidence interval of five out of nine included studies (151).

Overall, I-FABP might provide good specificity. If used in combination with another biomarker, the combined performance would be useful, but I-FABP cannot stand alone as an AIN biomarker.

6.2.7. ENDOTHELIN-1

The potent vasoconstrictor endothelin-1 showed good diagnostic performance with respect to AIN in surgical patients in our study. AUC and sensitivity were good; however, specificity was moderate. As the first study in endothelin-1 in a general surgical population, these findings are interesting and in accordance with the only human study in endothelin-1, although Groesdonk et al. explored endothelin-1 in NOMI patients alone (154). AUCs were almost similar in our study compared to the one by Groesdonk et al. However, they reported every second patient sample false-negative (sensitivity 51%) and specificity of 94%. In our study, we found the opposite with high sensitivity and low specificity, unveiling endothelin-1 as a potential screening test in the emergency department where AIN diagnosis is rare.

Subgroup analysis proposed endothelin-1 as being best in the portion of the AIN patients where diagnosis is most difficult–the vascular AIN patients (Table 5-8). Of course, the certainty of this statement is limited when only 10 vascular AIN patients were included. Additionally, whether endothelin-1 is an early biomarker was not sufficiently illuminated in this study. One might speculate that high-risk patients were late AIN because they were included after the AIN suspicion was raised. However, diagnostic performance in high-risk and nonhigh-risk patients displayed no difference.

6.2.8. I-FABP + ENDOTHELIN-1

I-FABP and endothelin-1 displayed high sensitivity and high specificity, respectively (171). This encouraged us to model the combined performance. Nevertheless, after leave-one-out cross-validation, the diagnostic performance equalled the performance of endothelin-1, and in nonhigh-risk patients, it was unchanged as well. In high-risk patients, the combined specificity increased but at the expense of sensitivity.

6.3. STRENGTHS AND LIMITATIONS

6.3.1. STUDY 1

Strengths

The strength of study one was, first, the inclusion of all vascular AIN patients with the aforementioned CT scan in the actual time range (169). This provided insight into the most difficult portion of AIN patients to diagnose, vascular AIN patients. Additionally, the study included patients where the suspicion was not raised or at least not mentioned in as much as 80% of the radiological referrals. This illuminates radiological findings in patients who are scarcely represented in the literature and patients not suspected to suffer from AIN.

Limitations

Study one was hampered by several limitations that must be addressed (169). The re-evaluation of the CT scans was unblinded and performed by two different gastrointestinal radiologists due to logistical reasons. This might have introduced bias in overestimating the amount of AIN findings. Additionally, AIN and control patients were included in 2006–2009, questioning the scanning quality and transferability to newer CT scanning technology. This might underestimate the findings in relation to the obstructive aetiology, such as an embolism. Thinner slices and higher resolution might secure a more accurate description of the vasculature and even compensate for some missed findings in noncontrast CT scans. Moreover, newer scanners may also detect unexpected findings in control patients.

Furthermore, the different age distributions between AIN and control patients might introduce bias from confounding overestimating the weight of the arteriosclerotic findings. Additionally, the adjustment for age in the analysis was performed linearly, leaving a risk of residual confounding. Adjustment with splines or a weighted analysis with propensity score was desirable but not possible due to the small sample size.

An unknown amount of confounding caused by unregistered disposing factors for AIN, different comorbidities, in particular cardiac disease, or lifestyle factors such as tobacco use might have affected the analysis.

Finally, the low number of AIN patients in the study weakens the conclusions and limited the possibility of adjusted analysis.

6.3.2. STUDY 2

Strengths

The main strength of Study 2 was the number of included nonhigh-risk patients (170). Unsuspected AIN patients with a blurred clinical and biochemical appearance are, as mentioned, the most difficult AIN patients to detect, as illustrated by the scarce research in this group.

Moreover, we unveiled D-lactate analysis as robust due to preanalytical handling. Additionally, the development of the automated setup introduced D-lactate analysis to the acute setting with quick reporting of the test results.

Limitations

Study two was intended to be a cross–sectional study in AIN patients in a general surgical population referred to the hospital with abdominal pain (170). The setup with inclusion of every adult patient referred to the surgical department in a single university hospital implicated some weaknesses. AIN patients referred to other departments were not included. Moreover, patients with severe physical conditions might not be included due to ethical considerations. This might explain the low number of AIN patients included in the group of nonhigh-risk patients and represents a potential selection bias of unknown direction and magnitude. Due to a small number of AIN patients in the initial inclusion period, a supplementary inclusion of high-risk patients suspected to suffer from AIN was performed. Therefore, inflating the prevalence of AIN in the cohort potentially biased PPV and NPV. Additionally, the low number of vascular AIN patients caused potential weak conclusions to this important group.

However, the main limitation in this study was the considerable lipemic interference excluding half of the AIN and control patients. Nevertheless, it did not change the main results and appears to be unrelated to the underlying pathophysiology in the control group, and an equally sized portion of AIN and control patients being affected. Additionally, when D-lactate was below the LoQ (55% in this study), it offered no clinical guidance regarding case status.

6.3.3. STUDY 3

Strengths

The main strength of Study three was the illumination of endothelin-1 in AIN patients in an unselected acute surgical population, which was to our knowledge, the first time in the literature (171). Additionally, the blood sample was drawn just after hospital contact, mimicking the clinical setting where future AIN biomarkers might accelerate the diagnostic workup, thus potentially lowering mortality. Finally, this study setup with drawing blood samples for later analysis made it possible to study a panel of potential AIN biomarkers revealing the diagnostic performance for the entire panel rather than separately for each parameter.

Limitations

Study three was a case–control study in the AIN patient group previously described in Study 2 and was thus hampered by several of the same limitations (170,171). The control patients were a subset of control patients from the Study 2 cohort and displayed the same age and sex distribution as the AIN patients. The low number of AIN patients limited the usefulness of the subgroup analysis, particularly in vascular AIN, which is the subgroup of particular concern.

Additionally, the preanalytical handling was potentially hampered by busy moments in the emergency department, preventing the analysis of several proposed biomarkers. Moreover, I-FABP and endothelin-1 were analysed in a manual manner, limiting the transferability to the acute setting where there is a need for quick reporting of test results. Furthermore, no international standardized methods and reference intervals were implemented for I-FABP and endothelin-1, potentially hampering the quality of the tests and contradicting the internationalization of the methods.

CHAPTER 7. CONCLUSION

AIN is a life-threatening disease with devastating high mortality rates above 50%. Vague symptom presentation in the initial hours after the obstructive event averts the initial suspicion and thus the subsequent timely diagnosis and treatment.

Diagnostic tools that might confirm the AIN diagnosis or arouse the suspicion of AIN within the first few hours after an obstructive event might be lifesaving.

An increasing rate of abdominal CT scans in acute patients has the potential to reveal early signs of AIN even in nonsuspected individuals with unspecific abdominal CT scans (169). Intestinal wall pathology, splanchnic vessel pathology and intestinal diameter are independent predictors of AIN observed in abdominal CT scans. Additionally, deciphering these findings implies that pneumatosis intestinalis, increased contrast enhancement in the bowel wall, inferior mesenteric artery arteriosclerosis and colonic contraction are predictors of AIN (169).

AIN biomarkers might be an objective tool for commencing AIN suspicion in the initial clinical evaluation. Thus, a broad range of parameters have been studied for decades. Standard biochemical parameters have failed to discriminate AIN patients from non-AIN patients. Nevertheless, L-lactate is widely used as an AIN biomarker despite conflicting evidence. Additionally, in our study, L-lactate failed to discriminate AIN patients from a wide range of acute surgical patients with low specificity and low AUC, disqualifying its use as an early AIN biomarker (171).

In recent decades, proposed biomarkers have been investigated. One of the most promising is D-lactate. In a large cross-sectional study, the discussion about D-lactate as an AIN biomarker was suggested settled (170). A poor AUC and sensitivity indicated the unsatisfactory diagnostic performance of D-lactate in discriminating AIN patients from a large group of acute non-AIN surgical patients.

Finally, I-FABP and endothelin-1 are promising AIN biomarkers. I-FABP showed good AUC and specificity, and endothelin-1 displayed good AUC and sensitivity in AIN patients compared to acute non-AIN surgical patients (171). The increased diagnostic performance of the two biomarkers in combination was eliminated in cross–validation, favouring endothelin-1, which displayed the highest AUC. Combining endothelin-1 analysed in an automated setup with a highly specific standard parameter might aid analytical and economic considerations.

CHAPTER 8. FUTURE PERSPECTIVES

The weak point in diagnosing AIN seems to be a combination of the first few hours from the obstructive event to the emergence of irreversible intestinal changes and the absence of AIN suspicion. This first mentioned timeframe is unchangeable, education and information might affect the latter, but the considerable resemblance between the dozens of non-AIN patients and the rare AIN patient is an obstacle to the commencement of AIN suspicion. Thus, searching for objective diagnostic tools is a continuing goal.

As mentioned, numerous studies have revealed potential biomarkers, but none have reached a clinical setting due to different obstacles. The search for biomarkers must be continued with a focus on early elevation after the obstructive event and the potential for routine analysis in hospital laboratories, ultimately leading to the development of rapid analytical testing for the prehospital setting.

Several of the proposed biomarkers are located in the intestinal lumen or intestinal wall. Considerable damage to the intestine is a prerequisite for leakage of the molecule to the circulation. Radiological findings such as reflex ileus suggest that pathophysiologic changes occur before considerable intestinal damage evolved, presumably neurologically mediated. Biomarkers in relation to neuropathological changes have been researched and might be of interest due to AIN (185,186).

A few scoring systems have been proposed in relation to AIN (91,187). In the era of artificial intelligence, it is appealing to extract data from large national databases and compose relevant scoring systems, although large databases are missing radiological findings. Future development and validation are warranted.

Finally, in light of early diagnostic tools in AIN patients, it is tempting to demand early high-quality CT scans in every patient referred to a gastrointestinal department with abdominal pain. Nevertheless, future research must continue to explore the relationship between this demand and the radiation dose in relation to cancer risk.

CHAPTER 9. REFERENCES

1. Cokkinis AJ. Mesenteric vascular occlusion. BAILLIERE, TINDALL & COX [Internet]. 1926 Mar 2; Available from: https://academic.oup.com/bjs/article/14/55/543/6229309

2. Ferris JAJ, Friesen JM. Definitions of ischaemia, infarction and necrosis. Forensic Science International. 1979 Jan 8;13(2):253–9.

3. Bala M, Kashuk J, Moore EE, Kluger Y, Biffl W, Gomes CA, et al. Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery. World Journal of Emergency Surgery. 2017;12(1).

4. Thomas JH, Blake K, Pierce GE, Hermreck AS, Seigel E, Gerwertz BL. The clinical course of asymptomatic mesenteric arterial stenosis. Journal of Vascular Surgery. 1998;27(5):840–4.

5. Rosenblum JD, Boyle CM, Schwartz LB. the Mesenteric Circulation. Surgical Clinics of North America. 1997;77(2):289–306.

6. Florim S, Almeida A, Rocha D, Portugal P. Acute mesenteric ischaemia: a pictorial review. Insights into Imaging. 2018 Oct;9(5):673–82.

7. Matsuda T, Sumi Y, Yamashita K, Hasegawa H, Yamamoto M, Matsuda Y, et al. Anatomical and embryological perspectives in laparoscopic complete mesocoloic excision of splenic flexure cancers. Surg Endosc. 2018 Mar;32(3):1202–8.

8. Oderich GS, de Souza LR. Pathophysiology. In: Oderich GS, editor. Mesenteric Vascular Disease [Internet]. New York, NY: Springer New York; 2015 [cited 2023 Feb 20]. p. 25–32. Available from: https://link.springer.com/10.1007/978-1-4939-1847-8_3

9. Chang M, Kistler EB, Schmid-Schönbein GW. Disruption of the mucosal barrier during gut ischemia allows entry of digestive enzymes into the intestinal wall. Shock. 2012;37(3):297–305.

10. Chiu CJ. Intestinal Mucosal Lesion in Low-Flow States. Archives of Surgery. 1970 Oct 1;101(4):478.

11. Ottinger LW. Mesenteric Ischemia. The New England Journal Of Medicine. 1982;

12. Menke J. Diagnostic Accuracy of Multidetector CT in Acute Mesenteric Ischemia: Systematic Review and Meta-Analysis. Radiology. 2010 Jul;256(1):93–101.

13. Björck M, Koelemay M, Acosta S, Bastos Goncalves F, Kölbel T, Kolkman JJ, et al. Editor's Choice – Management of the Diseases of Mesenteric Arteries and Veins: Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS). European Journal of Vascular and Endovascular Surgery. 2017;53(4):460–510.

14. Acosta S, Ögren M, Sternby NH, Bergqvist D, Björck M. Clinical implications for the management of acute thromboembolic occlusion of the superior mesenteric artery: Autopsy findings in 213 patients. Annals of Surgery. 2005;241(3):516–22.

15. Cappell MS. INTESTINAL (MESENTERIC) VASCULOPATHY I. Gastroenterology Clinics of North America. 1998 Dec;27(4):783–825.

16. Sise MJ. Acute mesenteric ischemia. The Surgical clinics of North America. 2014 Feb;94(1):165–81.

17. McKinsey JF, Gewertz BL. Acute mesenteric ischemia. The Surgical clinics of North America. 1997 Apr;77(2):307–18.

18. Mastoraki A. Mesenteric ischemia: Pathogenesis and challenging diagnostic and therapeutic modalities. World J Gastrointest Pathophysiol. 2016;7(1):125.

19. Wyers MC. Acute mesenteric ischemia: diagnostic approach and surgical treatment. Seminars in vascular surgery. 2010 Mar;23(1):9–20.

20. Lehtimäki TT, Kärkkäinen JM, Saari P, Manninen H, Paajanen H, Vanninen R. Detecting acute mesenteric ischemia in CT of the acute abdomen is dependent on clinical suspicion: Review of 95 consecutive patients. European Journal of Radiology. 2015;84(12):2444–53.

21. Carver TW, Vora RS, Taneja A. Mesenteric Ischemia. Critical Care Clinics. 2016;32(2):155–71.

22. Ghodasara N, Liddell R, Fishman EK, Johnson PT. High-Value Multidetector CT Angiography of the Superior Mesenteric Artery: What Emergency Medicine Physicians and Interventional Radiologists Need to Know. RadioGraphics. 2019 Mar;39(2):559–77.

23. Tamme K, Reintam Blaser A, Laisaar KT, Mändul M, Kals J, Forbes A, et al. Incidence and outcomes of acute mesenteric ischaemia: a systematic review and meta-analysis. BMJ open. 2022;12(10):e062846.

24. Acosta S, Ögren M, Sternby NH, Bergqvist D, Björck M. Incidence of acute thrombo-embolic occlusion of the superior mesenteric artery - A population-based study. European Journal of Vascular and Endovascular Surgery. 2004;27(2):145–50.

25. Block TA, Acosta S, Bjrck M. Endovascular and open surgery for acute occlusion of the superior mesenteric artery. Journal of Vascular Surgery. 2010;52(4):959–66.

26. Peoc'h K, Nuzzo A, Guedj K, Paugam C, Corcos O. Diagnosis biomarkers in acute intestinal ischemic injury: so close, yet so far. Clinical Chemistry and Laboratory Medicine (CCLM). 2018 Feb 23;56(3):373–85.

27. Nuzzo A, Maggiori L, Ronot M, Becq A, Plessier A, Gault N, et al. Predictive Factors of Intestinal Necrosis in Acute Mesenteric Ischemia: Prospective Study from an Intestinal Stroke Center. The American Journal of Gastroenterology. 2017;112(4):597–605.

28. Aschoff a J, Stuber G, Becker BW, Hoffmann MHK, Schmitz BL, Schelzig H, et al. Evaluation of acute mesenteric ischemia: accuracy of biphasic mesenteric multi-detector CT angiography. Abdominal imaging. 2009;34(3):345–57.

29. Ofer A, Abadi S, Nitecki S, Karram T, Kogan I, Leiderman M, et al. Multidetector CT angiography in the evaluation of acute mesenteric ischemia. European Radiology. 2009 Jan 9;19(1):24–30.

30. Yikilmaz A, Karahan OI, Senol S, Tuna IS, Akyildiz HY. Value of multislice computed tomography in the diagnosis of acute mesenteric ischemia. European Journal of Radiology. 2011;80(2):297–302.

31. Barmase M, Kang M, Wig J, Kochhar R, Gupta R, Khandelwal N. Role of multidetector CT angiography in the evaluation of suspected mesenteric ischemia. European journal of radiology. 2011 Dec;80(3):e582-7.

32. Klein HM, Lensing R, Klosterhalfen B, Töns C, Günther RW. Diagnostic imaging of mesenteric infarction. Radiology. 1995 Oct;197(1):79–82.

33. Kärkkäinen JM, Saari P, Kettunen HP, Lehtimäki TT, Vanninen R, Paajanen H, et al. Interpretation of Abdominal CT Findings in Patients Who Develop

Acute on Chronic Mesenteric Ischemia. Journal of Gastrointestinal Surgery. 2016 Apr 9;20(4):791–802.

34. Marston A. Diagnosis and management of intestinal ischaemia. Annals of the Royal College of Surgeons of England. 1972 Jan;50(1):29–44.

35. Herbert GS, Steele SR. Acute and Chronic Mesenteric Ischemia. Surgical Clinics of North America. 2007;87(5):1115–34.

36. Urbanavičius L. How to assess intestinal viability during surgery: A review of techniques. World Journal of Gastrointestinal Surgery. 2011;3(5):59.

37. Acosta S, Björck M. Acute thrombo-embolic occlusion of the superior mesenteric artery: A prospective study in a well defined population. European Journal of Vascular and Endovascular Surgery. 2003 Aug;26(2):179–83.

38. Oliva IB, Davarpanah AH, Rybicki FJ, Desjardins B, Flamm SD, Francois CJ, et al. ACR Appropriateness Criteria ® imaging of mesenteric ischemia. Abdominal imaging. 2013 Aug;38(4):714–9.

39. Ginsburg M, Obara P, Lambert DL, Hanley M, Steigner ML, Camacho MA, et al. ACR Appropriateness Criteria® Imaging of Mesenteric Ischemia. Journal of the American College of Radiology. 2018 Nov;15(11):S332–40.

40. Hawthorn BR, Ratnam LA. Acute mesenteric ischaemia: imaging and intervention. Clinical Radiology. 2020 May;75(5):398.e19-398.e28.

41. Shetty AS, Mellnick VM, Raptis C, Loch R, Owen J, Bhalla S. Limited utility of MRA for acute bowel ischemia after portal venous phase CT. Abdominal imaging. 2015 Oct;40(8):3020–8.

42. Acosta S, Wadman M, Syk I, Elmståhl S, Ekberg O. Epidemiology and prognostic factors in acute superior mesenteric artery occlusion. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2010 Apr;14(4):628–35.

43. Acosta S, Björnsson S, Ekberg O, Resch T. CT Angiography Followed by Endovascular Intervention for Acute Superior Mesenteric Artery Occlusion does not Increase Risk of Contrast-Induced Renal Failure. European Journal of Vascular and Endovascular Surgery. 2010;39(6):726–30.

44. Clair DG, Beach JM. Mesenteric Ischemia. Campion EW, editor. New England Journal of Medicine. 2016 Mar;374(10):959–68.

45. Augène E, Lareyre F, Chikande J, Guidi L, Mutambayi G, Lê CD, et al. Incidence of contrast-induced acute kidney injury in patients with acute mesenteric ischemia and identification of potential predictive factors. Vascular. 2022 Dec 13;30(6):1097–106.

46. De Simone B, Ansaloni L, Sartelli M, Gaiani F, Leandro G, De' Angelis GL, et al. Is the risk of contrast-induced nephropathy a real contraindication to perform intravenous contrast enhanced Computed Tomography for non-traumatic acute abdomen in Emergency Surgery Department? Acta bio-medica : Atenei Parmensis. 2018 Dec;89(9-S):158–72.

47. Mazzei MA, Mazzei FG, Marrelli D, Imbriaco G, Guerrini S, Vindigni C, et al. Computed Tomographic Evaluation of Mesentery. Journal of Computer Assisted Tomography. 2012;36(1):1–7.

48. Verdot P, Calame P, Winiszewski H, Grillet F, Malakhia A, Lakkis Z, et al. Diagnostic performance of CT for the detection of transmural bowel necrosis in non-occlusive mesenteric ischemia. European radiology. 2021 Sep;31(9):6835–45.

49. Brenner DJ, Hall EJ. Computed Tomography — An Increasing Source of Radiation Exposure. New England Journal of Medicine. 2007 Nov 29;357(22):2277–84.

50. Raman SP, Fishman EK. Computed Tomography Angiography of the Small Bowel and Mesentery. Radiologic clinics of North America. 2016 Jan;54(1):87–100.

51. Chai Y, Xing J, Lv P, Liang P, Xu H, Yue S, et al. Evaluation of ischemia and necrosis in adhesive small bowel obstruction based on CT signs: Subjective visual evaluation and objective measurement. European Journal of Radiology. 2022 Feb;147:110115.

52. Wiesner W, Khurana B, Ji H, Ros PR. CT of Acute Bowel Ischemia. Radiology. 2003 Mar;226(3):635–50.

53. Kirkpatrick IDC, Kroeker MA, Greenberg HM. Biphasic CT with Mesenteric CT Angiography in the Evaluation of Acute Mesenteric Ischemia: Initial Experience. Radiology. 2003 Oct;229(1):91–8.

54. Schieda N, Fasih N, Shabana W. Triphasic CT in the diagnosis of acute mesenteric ischaemia. European Radiology. 2013 Jul 8;23(7):1891–900.

55. Taourel PG, Deneuville M, Pradel J a, Régent D, Bruel JM. Acute mesenteric ischemia: diagnosis with contrast-enhanced CT. Radiology. 1996 Jun;199(3):632–6.

56. Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The Diagnosis of Acute Mesenteric Ischemia: A Systematic Review and Meta-analysis. Jones AE, editor. Academic Emergency Medicine. 2013 Nov;20(11):1087–100.

57. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. The Lancet. 2012 Aug;380(9840):499–505.

58. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013 May 21;346(may21 1):f2360–f2360.

59. Huang WY, Muo CH, Lin CY, Jen YM, Yang MH, Lin JC, et al. Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study. British Journal of Cancer. 2014 Apr 25;110(9):2354–60.

60. Meulepas JM, Ronckers CM, Smets AMJB, Nievelstein RAJ, Gradowska P, Lee C, et al. Radiation Exposure From Pediatric CT Scans and Subsequent Cancer Risk in the Netherlands. JNCI: Journal of the National Cancer Institute. 2019 Mar 1;111(3):256–63.

61. Hong JY, Han K, Jung JH, Kim JS. Association of Exposure to Diagnostic Low-Dose Ionizing Radiation With Risk of Cancer Among Youths in South Korea. JAMA Network Open. 2019 Sep 4;2(9):e1910584.

62. Ozasa K, Grant EJ, Kodama K. Japanese Legacy Cohorts: The Life Span Study Atomic Bomb Survivor Cohort and Survivors' Offspring. Journal of Epidemiology. 2018;28(4):162–9.

63. Lee KH, Lee S, Park JH, Lee SS, Kim HY, Lee WJ, et al. Risk of Hematologic Malignant Neoplasms From Abdominopelvic Computed Tomographic Radiation in Patients Who Underwent Appendectomy. JAMA Surgery. 2021 Apr 1;156(4):343.

64. Hendee WR, O'Connor MK. Radiation Risks of Medical Imaging: Separating Fact from Fantasy. Radiology. 2012 Aug;264(2):312–21.

65. Romano S, Niola R, Maglione F, Romano L. Small Bowel Vascular Disorders from Arterial Etiology and Impaired Venous Drainage. Radiologic Clinics of North America. 2008;46(5):891–908.

66. Srisajjakul S, Prapaisilp P, Bangchokdee S. Comprehensive review of acute small bowel ischemia: CT imaging findings, pearls, and pitfalls. Emergency Radiology. 2022 Jun 5;29(3):531–44.

67. Romano S, Lassandro F, Scaglione M, Romano L, Rotondo A, Grassi R. Ischemia and infarction of the small bowel and colon: Spectrum of imaging findings. Abdominal Imaging. 2006;31(3):277–92.

68. Kärkkäinen JM, Acosta S. Acute mesenteric ischemia (part I) – Incidence, etiologies, and how to improve early diagnosis. Best Practice & Research Clinical Gastroenterology. 2017 Feb;31(1):15–25.

69. Blachar A, Barnes S, Adam SZ, Levy G, Weinstein I, Precel R, et al. Radiologists' performance in the diagnosis of acute intestinal ischemia, using MDCT and specific CT findings, using a variety of CT protocols. Emergency Radiology. 2011;18(5):385–94.

70. Kanasaki S, Furukawa A, Fumoto K, Hamanaka Y, Ota S, Hirose T, et al. Acute Mesenteric Ischemia: Multidetector CT Findings and Endovascular Management. RadioGraphics. 2018;38(3).

71. Mirrahimi A, Gallienne C, Ghandehari H. An Overview of Acute Mesenteric Ischemia. Applied Radiology. 2021 Jan 1;50(1):10–8.

72. Atre ID, Eurboonyanun K, O'Shea A, Lahoud RM, Shih A, Kalva S, et al. Predictors of transmural intestinal necrosis in patients presenting with acute mesenteric ischemia on computed tomography. Abdominal Radiology. 2022 May 7;47(5):1636–43.

73. Sheedy SP, Earnest F, Fletcher JG, Fidler JL, Hoskin TL. CT of Small-Bowel Ischemia Associated with Obstruction in Emergency Department Patients: Diagnostic Performance Evaluation. Radiology. 2006 Dec;241(3):729–36.

74. Wadman M, Block T, Ekberg O, Syk I, Elmståhl S, Acosta S. Impact of MDCT with intravenous contrast on the survival in patients with acute superior mesenteric artery occlusion. Emergency Radiology. 2010;17(3):171–8.

75. Zeng Y, Yang F, Hu X, Zhu F, Chen W, Lin W. Radiological predictive factors of transmural intestinal necrosis in acute mesenteric ischemia: systematic

review and meta-analysis. European Radiology [Internet]. 2022 Nov 30; Available from: https://link.springer.com/10.1007/s00330-022-09258-5

76. Wiesner W, Hauser A, Steinbrich W. Accuracy of multidetector row computed tomography for the diagnosis of acute bowel ischemia in a non-selected study population. European radiology. 2004 Dec;14(12):2347–56.

77. Chen YC, Huang TY, Chen RC, Tsai SH, Chang WC, Fan HL, et al. Comparison of Ischemic and Nonischemic Bowel Segments in Patients with Mesenteric Ischemia: Multidetector Row Computed Tomography Findings and Measurement of Bowel Wall Attenuation Changes. Mayo Clinic Proceedings. 2016;91(3):316–28.

78. Reginelli A, Iacobellis F, Berritto D, Gagliardi G, Di Grezia G, Rossi M, et al. Mesenteric ischemia: The importance of differential diagnosis for the surgeon. BMC Surgery. 2013;13(SUPPL.2).

79. Prakash VS, Marin M, Faries PL. Acute and Chronic Ischemic Disorders of the Small Bowel. Current Gastroenterology Reports. 2019;21(6):1–6.

80. Millet I, Taourel P, Ruyer A, Molinari N. Value of CT findings to predict surgical ischemia in small bowel obstruction: A systematic review and meta-analysis. European Radiology. 2015;25(6):1823–35.

81. Davarpanah AH, Ghamari Khameneh A, Khosravi B, Mir A, Saffar H, Radmard AR. Many faces of acute bowel ischemia: overview of radiologic staging. Insights into Imaging [Internet]. 2021;12(1). Available from: https://doi.org/10.1186/s13244-021-00985-9

82. Kernagis LY, Levine MS, Jacobs JE. Pneumatosis intestinalis in patients with ischemia: Correlation of CT findings with viability of the bowel. American Journal of Roentgenology. 2003;180(3):733–6.

83. Mazzei MA, Volterrani L. Nonocclusive mesenteric ischaemia: think about it. La Radiologia medica. 2015 Jan;120(1):85–95.

84. Murphy KP, Twomey M, McLaughlin PD, O'Connor OJ, Maher MM. Imaging of Ischemia, Obstruction and Infection in the Abdomen. Radiologic clinics of North America. 2015;53(4):847–69.

85. Romano S, Scaglione M, Gatta G, Lombardo P, Stavolo C, Romano L, et al. Association of splenic and renal infarctions in acute abdominal emergencies. European Journal of Radiology. 2004;50(1):48–58.

86. World Health Organization. World Health Organization & International Programme on Chemical Safety. (2001). Biomarkers in risk assessment : validity and validation. Retrieved from http://www.inchem.org/documents/ehc/ehc/ehc222.htm. 2001;

87. Devaraj S, Singh U, Jialal I. The Evolving Role of C-Reactive Protein in Atherothrombosis. Clinical Chemistry. 2009 Feb 1;55(2):229–38.

88. Gulhar R, Ashraf MA, Jialal I. Physiology, Acute Phase Reactants [Internet]. StatPearls. 2022. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16252337

89. Kärkkäinen JM. Acute Mesenteric Ischemia: A Challenge for the Acute Care Surgeon. Scandinavian Journal of Surgery. 2021 Jun 19;110(2):150–8.

90. Salem TA, Molloy RG, O'Dwyer PJ. Prospective study on the role of C-reactive protein (CRP) in patients with an acute abdomen. Annals of the Royal College of Surgeons of England. 2007;89(3):233–7.

91. Khan SM, Emile SH, Wang Z, Agha MA. Diagnostic accuracy of hematological parameters in Acute mesenteric ischemia-A systematic review. International Journal of Surgery. 2019;66(February):18–27.

92. Acosta S, Nilsson TK, Björck M. D-dimer testing in patients with suspected acute thromboembolic occlusion of the superior mesenteric artery. The British journal of surgery. 2004 Aug;91(8):991–4.

93. Derikx JPM, Schellekens DHSM, Acosta S. Serological markers for human intestinal ischemia: A systematic review. Best Practice & Research Clinical Gastroenterology. 2017 Feb;31(1):69–74.

94. Demir IE, Ceyhan GO, Friess H. Beyond Lactate: Is There a Role for Serum Lactate Measurement in Diagnosing Acute Mesenteric Ischemia? Digestive Surgery. 2012 Jan;29(3):226–35.

95. Glenister KM, Corke CF. Infarcted intestine: a diagnostic void. ANZ journal of surgery. 2004 Apr;74(4):260–5.

96. Lange H, Jäckel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. The European journal of surgery = Acta chirurgica. 160(6–7):381–4.

97. Montagnana M, Danese E, Lippi G. Biochemical markers of acute intestinal ischemia: possibilities and limitations. Annals of translational medicine. 2018 Sep;6(17):341.

98. Acosta S, Nilsson TK, Malina J, Malina M. L-lactate after embolization of the superior mesenteric artery. The Journal of surgical research. 2007 Dec;143(2):320–8.

99. Kurimoto Y, Kawaharada N, Ito T, Morikawa M, Higami T, Asai Y. An experimental evaluation of the lactate concentration following mesenteric ischemia. Surgery Today. 2008;38(10):926–30.

100. Aydin B, Ozban M, Serinken M, Kaptanoglu B, Demirkan NC, Aydin C. The place of D-dimer and L-lactate levels in the early diagnosis of acute mesenteric ischemia. Bratislava Medical Journal. 2015;116(05):343–50.

101. Novotny T, Staffa R, Tomandl J, Krivka T, Slaby O, Kubicek L, et al. l-lactate kinetics after abdominal aortic surgery and intestinal ischemia – An observational cohort study. International Journal of Surgery. 2022 Feb;98:106220.

102. Brillantino A, Iacobellis F, Renzi A, Nasti R, Saldamarco L, Grillo M, et al. Diagnostic value of arterial blood gas lactate concentration in the different forms of mesenteric ischemia. European journal of trauma and emergency surgery : official publication of the European Trauma Society. 2018 Apr;44(2):265–72.

103. Yang S, Fan X, Ding W, Liu B, Meng J, Wang K, et al. D-dimer as an early marker of severity in patients with acute superior mesenteric venous thrombosis. Medicine. 2014 Dec;93(29):e270.

104. Matsumoto S, Shiraishi A, Kojima M, Funaoka H, Funabiki T, Saida T, et al. Comparison of diagnostic accuracy for nonocclusive mesenteric ischemia in models with biomarkers including intestinal fatty acid-binding protein in addition to clinical findings. Journal of Trauma and Acute Care Surgery. 2019;86(2):220–5.

105. Ambe PC, Kang K, Papadakis M, Zirngibl H. Can the Preoperative Serum Lactate Level Predict the Extent of Bowel Ischemia in Patients Presenting to the Emergency Department with Acute Mesenteric Ischemia? BioMed Research International. 2017;2017:1–5.

106. Mothes H, Koeppen J, Bayer O, Richter M, Kabisch B, Schwarzkopf D, et al. Acute mesenteric ischemia following cardiovascular surgery - A nested case-

control study. International journal of surgery (London, England). 2016;26(2016):79–85.

107. Otto CC, Czigany Z, Heise D, Bruners P, Kotelis D, Lang SA, et al. Prognostic Factors for Mortality in Acute Mesenteric Ischemia. Journal of Clinical Medicine. 2022;11(13):1–13.

108. van der Voort PHJ, Westra B, Wester JPJ, Bosman RJ, van Stijn I, Haagen IA, et al. Can serum L-lactate, D-lactate, creatine kinase and I-FABP be used as diagnostic markers in critically ill patients suspected for bowel ischemia. BMC anesthesiology. 2014;14:111.

109. Destek S, Yabacı A, Abik YN, Gül VO, Değer KC. Predictive and prognostic value of L-lactate, D-dimer, leukocyte, C-reactive protein and neutrophil/lymphocyte ratio in patients with acute mesenteric ischemia. Ulusal Travma ve Acil Cerrahi Dergisi. 2020 Jan;26(1):86–94.

110. Thuijls G, Wijck K van, Grootjans J, Derikx JPM, van Bijnen AA, Heineman E, et al. Early Diagnosis of Intestinal Ischemia Using Urinary and Plasma Fatty Acid Binding Proteins. Annals of Surgery. 2011 Feb;253(2):303–8.

111. Studer P, Vaucher A, Candinas D, Schnüriger B. The Value of Serial Serum Lactate Measurements in Predicting the Extent of Ischemic Bowel and Outcome of Patients Suffering Acute Mesenteric Ischemia. Journal of Gastrointestinal Surgery. 2015;19(4):751–5.

112. Meyer ZC, Schreinemakers JMJ, Mulder PGH, de Waal R a L, Ermens A a M, van der Laan L. Determining the clinical value of lactate in surgical patients on the intensive care unit. The Journal of surgical research. 2013 Aug;183(2):814–20.

113. Collange O, Lopez M, Lejay A, Pessaux P, Ouattara A, Dewitte A, et al. Serum lactate and acute mesenteric ischaemia: An observational, controlled multicentre study. Anaesthesia Critical Care and Pain Medicine. 2022;41(6).

114. Leone M, Bechis C, Baumstarck K, Ouattara A, Collange O, Augustin P, et al. Outcome of acute mesenteric ischemia in the intensive care unit: a retrospective, multicenter study of 780 cases. Intensive Care Medicine. 2015;41(4):667–76.

115. Reintam Blaser A, Forbes A, Björck M. Acute mesenteric ischaemia. Current Opinion in Critical Care. 2022;28(6):702–8.

116. Reintam Blaser A, Acosta S, Arabi YM. A clinical approach to acute mesenteric ischemia. Current opinion in critical care. 2021 Apr;27(2):183–92.

117. Acosta S. Mesenteric ischemia. Current Opinion in Critical Care. 2015 Apr;21(2):171–8.

118. Memet O, Zhang L, Shen J. Serological biomarkers for acute mesenteric ischemia. Annals of translational medicine. 2019 Aug;7(16):394.

119. Powell A, Armstrong P. Plasma biomarkers for early diagnosis of acute intestinal ischemia. Seminars in Vascular Surgery. 2014;27(3–4):170–5.

120. Bala M, Catena F, Kashuk J, De Simone B, Gomes CA, Weber D, et al. Acute mesenteric ischemia: updated guidelines of the World Society of Emergency Surgery. World Journal of Emergency Surgery. 2022 Oct 19;17(1):54.

121. Tilsed JVT, Casamassima A, Kurihara H, Mariani D, Martinez I, Pereira J, et al. ESTES guidelines: acute mesenteric ischaemia. European Journal of Trauma and Emergency Surgery. 2016;42(2):253–70.

122. Aboyans V, Ricco JB, Bartelink MLEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). European Heart Journal. 2018;39(9):763–816.

123. Acosta S, Block T, Björnsson S, Resch T, Björck M, Nilsson T. Diagnostic pitfalls at admission in patients with acute superior mesenteric artery occlusion. Journal of Emergency Medicine. 2012;42(6):635–41.

124. Oh MS, Phelps KR, Traube M, Barbosa-Saldivar JL, Boxhill C, Carroll HJ. D-Lactic Acidosis in a Man with the Short-Bowel Syndrome. New England Journal of Medicine. 1979 Aug 2;301(5):249–52.

125. Dohle DS, Bestendonk C, Petrat F, Tsagakis K, Wang M, Strucksberg KH, et al. Serum markers for early detection of patients with mesenteric ischemia after cardiac surgery. Innovative Surgical Sciences. 2020;3(4):277–83.

126. Murray MJ, Gonze MD, Nowak LR, Cobb CF. Serum D(−)-lactate levels as an aid to diagnosing acute intestinal ischemia. The American Journal of Surgery. 1994 Jun;167(6):575–8.

127. Levitt MD, Levitt DG. Quantitative evaluation of d-lactate pathophysiology: New insights into the mechanisms involved and the many areas in need of

further investigation. Clinical and Experimental Gastroenterology. 2020;13:321–37.

128. Guo YY, Liu ML, He X di, Jiang CQ, Liu RL. Functional changes of intestinal mucosal barrier in surgically critical patients. World journal of emergency medicine. 2010;1(3):205–8.

129. Shi H, Wu B, Wan J, Liu W, Su B. The role of serum intestinal fatty acid binding protein levels and D-lactate levels in the diagnosis of acute intestinal ischemia. Clinics and research in hepatology and gastroenterology. 2015;39(3):373–8.

130. de Vrese M, Koppenhoefer B, Barth CA. D-lactic acid metabolism after an oral load of dl-lactate. Clinical Nutrition. 1990 Feb;9(1):23–8.

131. Monroe GR, van Eerde AM, Tessadori F, Duran KJ, Savelberg SMC, van Alfen JC, et al. Identification of human D lactate dehydrogenase deficiency. Nature Communications. 2019;10(1).

132. Nielsen C, Lindholt JS, Erlandsen EJ, Mortensen FV. D-Lactate As a Marker of Venous-Induced Intestinal Ischemia: an Experimental Study in Pigs. International journal of surgery (London, England). 2011 Jan;9(5):428–32.

133. Poeze, Froon, Greve, Ramsay. D-lactate as an early marker of intestinal ischaemia after ruptured abdominal aortic aneurysm repair. British Journal of Surgery. 1998 Sep;85(9):1221–4.

134. Assadian a, Assadian O, Senekowitsch C, Rotter R, Bahrami S, Fürst W, et al. Plasma D-lactate as a potential early marker for colon ischaemia after open aortic reconstruction. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2006 May;31(5):470–4.

135. Evennett NJ, Petrov MS, Mittal A, Windsor JA. Systematicreview and pooled estimates for the diagnostic accuracy of serological markers for intestinal ischemia. World Journal of Surgery. 2009 Jul;33(7):1374–83.

136. Nielsen C, Mortensen FV, Erlandsen EJ, Lindholt JS. L- and D-lactate as biomarkers of arterial-induced intestinal ischemia: an experimental study in pigs. International journal of surgery (London, England). 2012 Jan;10(6):296–300.

137. Nuzzo A, Guedj K, Curac S, Hercend C, Bendavid C, Gault N, et al. Accuracy of citrulline, I-FABP and d-lactate in the diagnosis of acute mesenteric ischemia. Sci Rep. 2021 Sep 23;11(1):18929.

138. Block T, Nilsson TK, Björck M, Acosta S. Diagnostic accuracy of plasma biomarkers for intestinal ischaemia. Scandinavian journal of clinical and laboratory investigation. 2008 Jan;68(3):242–8.

139. Isfordink CJ, Dekker D, Monkelbaan JF. Clinical value of serum lactate measurement in diagnosing acute mesenteric ischaemia. The Netherlands journal of medicine. 2018 Mar;76(2):60–4.

140. Deen R, Sia ZK. Review article: Acute superior mesenteric vessel ischaemia: A review of clinical practice and biomarkers. EMA - Emergency Medicine Australasia. 2022;(November).

141. Treskes N, Persoon AM, Zanten ARHV, van Zanten ARH. Diagnostic accuracy of novel serological biomarkers to detect acute mesenteric ischemia: a systematic review and meta-analysis. Internal and Emergency Medicine. 2017 Sep;12(6):821–36.

142. Hong J, Gilder E, Blenkiron C, Jiang Y, Evennett NJ, Petrov MS, et al. Nonocclusive mesenteric infarction after cardiac surgery: potential biomarkers. Journal of Surgical Research. 2017;211:21–9.

143. Ockner RK, Manning JA. Fatty acid binding protein in small intestine. Identification, isolation, and evidence for its role in cellular fatty acid transport. Journal of Clinical Investigation. 1974;54(2):326–38.

144. Sweetser DA, Birkenmeier EH, Klisak IJ, Zollman S, Sparkes RS, Mohandas T, et al. The human and rodent intestinal fatty acid binding protein genes: A comparative analysis of their structure, expression, and linkage relationships. Journal of Biological Chemistry. 1987;262(33):16060–71.

145. Kanda T, Nakatomi Y, Ishikawa H, Hitomi M, Matsubara Y, Ono T, et al. Intestinal fatty acid-binding protein as a sensitive marker of intestinal ischemia. Digestive diseases and sciences. 1992 Sep;37(9):1362–7.

146. Kanda T, Fujii H, Fujita M, Sakai Y, Ono T, Hatakeyama K. Intestinal fatty acid binding protein is available for diagnosis of intestinal ischaemia: Immunochemical analysis of two patients with ischaemic intestinal diseases. Gut. 1995;36(5):788–91.

147. Matsumoto S, Sekine K, Funaoka H, Yamazaki M, Shimizu M, Hayashida K, et al. Diagnostic performance of plasma biomarkers in patients with acute intestinal ischaemia. The British journal of surgery. 2014 Feb;101(3):232–8.

148. Derikx JPM, Matthijsen RA, de Bruïne AP, van Bijnen AA, Heineman E, van Dam RM, et al. Rapid reversal of human intestinal ischemia-reperfusion induced damage by shedding of injured enterocytes and reepithelialisation. PLoS ONE. 2008;3(10).

149. Vermeulen Windsant IC, Hellenthal F a, Derikx JPM, Prins MH, Buurman W a, Jacobs MJ, et al. Circulating intestinal fatty acid-binding protein as an early marker of intestinal necrosis after aortic surgery: a prospective observational cohort study. Annals of surgery. 2012 Apr;255(4):796–803.

150. Bourcier S, Ulmann G, Jamme M, Savary G, Paul M, Benghanem S, et al. A multicentric prospective observational study of diagnosis and prognosis features in ICU mesenteric ischemia: the DIAGOMI study. Ann Intensive Care. 2022 Dec 17;12(1):113.

151. Sun DL, Cen YY, Li SM, Li WM, Lu QP, Xu PY. Accuracy of the serum intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: A meta-analysis. Scientific Reports. 2016;6(September):1–7.

152. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature. 1988 Mar;332(6163):411–5.

153. Barton M, Yanagisawa M. Endothelin: 20 Years from discovery to therapy. Canadian Journal of Physiology and Pharmacology. 2008;86(8):485–98.

154. Groesdonk HV, Raffel M, Speer T, Bomberg H, Schmied W, Klingele M, et al. Elevated endothelin-1 level is a risk factor for nonocclusive mesenteric ischemia. Journal of Thoracic and Cardiovascular Surgery. 2015;149(5):1436-1442.e2.

155. Bomberg H, Bierbach B, Flache S, Wagner I, Gläser L, Groesdonk HV, et al. Endothelin and vasopressin influence splanchnic blood flow distribution during and after cardiopulmonary bypass. The Journal of Thoracic and Cardiovascular Surgery. 2013 Feb;145(2):539–47.

156. Ucar BI, Erikci A, Kosemehmetoglu K, Ozkul C, Iskit AB, Ucar G, et al. Effects of endothelin receptor blockade and COX inhibition on intestinal I/R injury in a rat model: Experimental research. International Journal of Surgery. 2020 Nov;83:89–97.

157. Dong F, Zhang X, Wold LE, Ren Q, Zhang Z, Ren J. Endothelin-1 enhances oxidative stress, cell proliferation and reduces apoptosis in human umbilical vein endothelial cells: Role of ET B receptor, NADPH oxidase and caveolin-1. British Journal of Pharmacology. 2005;145(3):323–33.

158. Diep QN, Intengan HD, Schiffrin EL. by Inhibition of Caspase 3. 2000;1:287–91.

159. Sharifi AM, Schiffrin EL. Apoptosis in aorta of deoxycorticosterone acetate-salt hypertensive rats: Effect of endothelin receptor antagonism. Journal of Hypertension. 1997;15(12):1441–8.

160. Okazawa M, Shiraki T, Ninomiya H, Kobayashi S, Masaki T. Endothelin-induced apoptosis of A375 human melanoma cells. Journal of Biological Chemistry. 1998;273(20):12584–92.

161. Wang JY, Cheng KI, Yu FJ, Tsai HL, Huang TJ, Hsieh JS. Analysis of the correlation of plasma NO and ET-1 levels in rats with acute mesenteric ischemia. Journal of Investigative Surgery. 2006;19(3):155–61.

162. Bomberg H, Bierbach B, Flache S, Novák M, Schäfers HJ, Menger MD. Dobutamine versus Vasopressin After Mesenteric Ischemia. Journal of Surgical Research. 2019;235:410–23.

163. Gearhart SL, Delaney CP, Senagore AJ, Banbury MK, Remzi FH, Kiran RP, et al. Prospective assessment of the predictive value of alpha-glutathione S-transferase for intestinal ischemia. The American surgeon. 2003 Apr;69(4):324–9; discussion 329.

164. Xiong RG, Zhou DD, Wu SX, Huang SY, Saimaiti A, Yang ZJ, et al. Health Benefits and Side Effects of Short-Chain Fatty Acids. Foods. 2022 Sep 15;11(18):2863.

165. Li H, Herrmann T, Seeßle J, Liebisch G, Merle U, Stremmel W, et al. Role of fatty acid transport protein 4 in metabolic tissues: insights into obesity and fatty liver disease. Bioscience Reports. 2022 Jun 30;42(6):BSR20211854.

166. Koepsell H. Glucose transporters in the small intestine in health and disease. Pflugers Arch - Eur J Physiol. 2020 Sep;472(9):1207–48.

167. Gunduz A, Turkmen S, Turedi S, Mentese A, Yulug E, Ulusoy H, et al. Time-dependent variations in ischemia-modified albumin levels in mesenteric ischemia. Academic Emergency Medicine. 2009;16(6):539–43.

168. Gunduz A, Turedi S, Mentese A, Karahan SC, Hos G, Tatli O, et al. Ischemia-modified albumin in the diagnosis of acute mesenteric ischemia: a preliminary study. The American journal of emergency medicine. 2008 Feb;26(2):202–5.

169. Straarup, D; Gotschalck KA; Christensen PA; Krarup H; Lundbye-Christensen S; Handberg Aa; Thorlacius-Ussing O D, Gotschalck KA, Mikalone R, Thorlacius-Ussing O. Preoperative findings on non-specific CT in patients with primary acute intestinal ischemia: a case–control study. European Journal of Trauma and Emergency Surgery [Internet]. 2021;(0123456789). Available from: https://doi.org/10.1007/s00068-021-01741-w

170. Straarup, D; Gotschalck KA; Christensen PA; Rasmussen RW; Krarup H; Lundbye-Christensen S; Handberg Aa; Thorlacius-Ussing O. Exploring D-lactate as a biomarker for acute intestinal necrosis: A cross-sectional prospective study of 2958 pateints. In press.

171. Straarup, D; Gotschalck KA; Christensen PA; Krarup H; Lundbye-Christensen S; Handberg Aa; Thorlacius-Ussing O CP et al. Exploring I-FABP, endothelin-1 and L-lactate as biomarkers of acute intestinal necrosis: A case–control study. Scandinavian Journal of Gastroenterology [Internet]. 2023 Jul 4;1–7. Available from: https://www.tandfonline.com/doi/full/10.1080/00365521.2023.2229930

172. Rasmussen RW, Straarup D, Thorlacius-Ussing O, Handberg A, Christensen PA. Fully automatic d-lactate assay using a modified commercially available method. Scandinavian Journal of Clinical and Laboratory Investigation. 2021 Jul;81(4):312–7.

173. Akyildiz H, Akcan A, Oztürk A, Sozuer E, Kucuk C, Karahan I. The correlation of the D-dimer test and biphasic computed tomography with mesenteric computed tomography angiography in the diagnosis of acute mesenteric ischemia. American journal of surgery. 2009 Apr;197(4):429–33.

174. Salhotra N, Dhawan R, Galhotra A, Galhotra A, Kakkar C, Dhanota DPS, et al. Role of Multidetector Computed Tomography in Patients of Acute Mesenteric Ischaemia and its Comparison with Clinicosurgical Outcome: A Cross-sectional Study. Journal of Clinical and Diagnostic Research. 2021;30–3.

175. Sala E, Watson CJE, Beadsmoore C, Groot-Wassink T, Fanshawe TR, Smith JC, et al. A randomized, controlled trial of routine early abdominal computed tomography in patients presenting with non-specific acute abdominal pain. Clinical Radiology. 2007;62(10):961–9.

176. Henes FO, Pickhardt PJ, Herzyk A, Lee SJ, Motosugi U, Derlin T, et al. CT angiography in the setting of suspected acute mesenteric ischemia: prevalence

of ischemic and alternative diagnoses. Abdominal Radiology. 2017 Apr 24;42(4):1152–61.

177. Tengberg LT, Bay-Nielsen M, Bisgaard T, Cihoric M, Lauritsen ML, Foss NB, et al. Multidisciplinary perioperative protocol in patients undergoing acute high-risk abdominal surgery. British Journal of Surgery. 2017;104(4):463–71.

178. Koami H, Isa T, Ishimine T, Kameyama S, Matsumura T, Yamada KC, et al. Risk factors for bowel necrosis in patients with hepatic portal venous gas. Surgery Today. 2015 Feb 1;45(2):156–61.

179. Davenport MS, Perazella MA, Yee J, Dillman JR, Fine D, McDonald RJ, et al. Use of Intravenous Iodinated Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation. Radiology. 2020 Mar;294(3):660–8.

180. Moschetta M, Telegrafo M, Rella L, Stabile Ianora AA, Angelelli G. Multi-detector CT features of acute intestinal ischemia and their prognostic correlations. World journal of radiology. 2014;6(5):130–8.

181. Saba L, Mallarini G. Computed tomographic imaging findings of bowel ischemia. Journal of computer assisted tomography. 2008;32(3):329–40.

182. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk. Journal of the American College of Cardiology. 2014 Jul;63(25):2935–59.

183. Solé-Enrech G, Cano-Corres R, Aparicio-Calvente MI, Spataro N. Elimination of lipaemic interference by high-speed centrifugation. Biochemia medica. 2023;33(1):010703.

184. Nielsen C, Pedersen LT, Lindholt JS, Mortensen FV, Erlandsen EJ. An automated plasma D-lactate assay with a new sample preparation method to prevent interference from L-lactate and L-lactate dehydrogenase. Scandinavian journal of clinical and laboratory investigation. 2011 Oct;71(6):507–14.

185. Abdelhak A, Foschi M, Abu-Rumeileh S, Yue JK, D'Anna L, Huss A, et al. Blood GFAP as an emerging biomarker in brain and spinal cord disorders. Nature Reviews Neurology. 2022;18(3):158–72.

186. Klein J, Schneider R, Wehner S, Schäfer N, Kalff J, von Websky M. The Role of Enteric Glia Cells in Intestinal Regeneration After Mesenteric Ischemia and Reperfusion. Transplantation. 2017 Jun;101(6S2):S26–7.

187. Zogheib E, Cosse C, Sabbagh C, Marx S, Caus T, Henry M, et al. Biological scoring system for early prediction of acute bowel ischemia after cardiac surgery: the PALM score. Annals of Intensive Care [Internet]. 2018;8(1). Available from: https://doi.org/10.1186/s13613-018-0395-5

APPENDICES

I. Straarup D, Gotschalck KA, Mikalone R, *et al.* Preoperative findings on non-specific CT in patients with primary acute intestinal ischemia: a case–control study. *European Journal of Trauma and Emergency Surgery* Published Online First: 2021. doi:10.1007/s00068-021-01741-w
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II. Straarup D, Gotschalck KA, Christensen PA, et al. Exploring D-lactate as a biomarker for acute intestinal necrosis in 2958 patients: a prospective cross-sectional study. In review.

III. Straarup, D; Gotschalck, KA; Christensen, PA; Krarup, H; Lundbye-Christensen, S; Handberg, A; Thorlacius-Ussing, O. Exploring I-FABP, endothelin-1 and L-lactate as biomarkers of acute intestinal necrosis: a case-control study. Scand J Gastroenterol. 2023 Jul 4:1-7. doi: 10.1080/00365521.2023.2229930. Epub ahead of print. PMID: 37403410.

”…occlusion of the mesenteric vessels is apt to be regarded as one of those conditions of which diagnosis is impossible, the prognosis hopeless and the treatment almost useless.”

A. J. Cokkinis, 1926

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