

Mortality in Patients Who Underwent Computed Tomography Angiography for a Suspected Acute Mesenteric Ischemia as a Final Alternative Diagnosis

Noy Nachmias-Peiser MD^{1,3}, Shelly Soffer MD^{1,3}, Nir Horesh MD^{2,3}, Galit Zlotnick MD^{1,3}, Marianne Michal Amitai MD^{1,3}, and Eyal Klang MD^{1,3}

Departments of ¹Radiology and ²Surgery and Transplantation B, Sheba Medical Center, Tel Hashomer, Israel

³Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT

Background: Acute mesenteric ischemia (AMI) is a medical condition with high levels of morbidity and mortality. However, most patients suspected of AMI will eventually have a different diagnosis. Nevertheless, these patients have a high risk for co-morbidities.

Objectives: To analyze patients with suspected AMI with an alternative final diagnosis, and to evaluate a machine learning algorithm for prognosis prediction in this population.

Methods: In a retrospective search, we retrieved patient charts of those who underwent computed tomography angiography (CTA) for suspected AMI between January 2012 and December 2015. Non-AMI patients were defined as patients with negative CTA and a final clinical diagnosis other than AMI. Correlation of past medical history, laboratory values, and mortality rates were evaluated. We evaluated gradient boosting (XGBoost) model for mortality prediction.

Results: The non-AMI group comprised 325 patients. The two most common groups of diseases included gastrointestinal (33%) and biliary-pancreatic diseases (27%). Mortality rate was 24.6% for the entire cohort. Medical history of chronic kidney disease (CKD) had higher risk for mortality (odds ratio 2.2). Laboratory studies revealed that lactate dehydrogenase (LDH) had the highest diagnostic ability for predicting mortality in the entire cohort (AUC 0.70). The gradient boosting model showed an area under the curve of 0.82 for predicting mortality.

Conclusions: Patients with suspected AMI with an alternative final diagnosis showed a 25% mortality rate. A past medical history of CKD and elevated LDH were associated with increased mortality. Non-linear machine learning algorithms can augment single variable inputs for predicting mortality.

IMAJ 2022; 24: 828–833

KEY WORDS: acute mesenteric ischemia (AMI), machine learning, mortality, non-acute mesenteric ischemia (non-AMI), prognosis prediction

Acute mesenteric ischemia (AMI) is a catastrophic medical condition with high morbidity and mortality [1,2]. This condition is a clinical challenge, as it is an infrequent diagnosis with no pathognomonic factors, such as clinical symptoms or laboratory tests [2,3].

One of the main diagnostic markers that has been investigated regarding mesenteric ischemia is serum lactate. Although lactate is a sensitive biomarker for AMI it has low specificity. Many studies have found high levels of lactate in different cases of abdominal complaints and acute abdomen [4–6]. Nonetheless, in these studies, high levels of lactate were found to be a predicting factor for mortality regardless of the final diagnosis [4–6].

In practice, most patients admitted to the emergency department with suspected AMI, eventually are diagnosed with different medical conditions [2,7].

Patients suspected of an AMI are mostly older than 65 years with co-morbidities such as hypertension, arrhythmias, cerebral vascular disease, and diabetes mellitus [3]; hence, they are at a high risk for morbidity and mortality.

Recent advancements in the field of artificial intelligence (AI) have enabled the development of prognostic models that can help individualized patient care. AI is a broad term that describes computer algorithms that solve problems that usually require human intelligence [8]. Machine learning (ML) is a subclass of AI that gives computers the ability to learn without being explicitly programmed [9].

The aims of this study were to analyze patients initially suspected of AMI, but with a different final diagnosis and to evaluate ML algorithms for predicting prognosis in this population.

PATIENTS AND METHODS

Institutional review board approval was granted for this study, and informed consent was waived by the committee.

This retrospective study included all patients with suspected AMI who underwent an abdominal computed tomography angiography (CTA) examination in one tertiary hospital between January 2012 and December 2015. We retrieved the following

variables: demographic data, past medical history, recorded laboratory values, duration of hospitalization, final diagnosis given during hospitalization, and mortality. CTA interpretations were also retrieved. Surgery reports were obtained for patients who underwent surgery.

The definition of non-AMI in our study was based on an integration of negative CTA findings and documentation of final diagnosis other than an acute mesenteric event. In cases of discrepancies between CTA interpretation and final diagnosis, two radiologists re-interpreted the CTA findings to ascertain that there were no radiological findings for AMI.

We defined patients with an acute mesenteric event as the AMI group and patients without an acute mesenteric event as the non-AMI group.

Patients whose records provided insufficient information regarding hospitalization and laboratory tests were excluded from the study. Furthermore, all laboratory results included in this study were with the closest proximity to the CTA of each patient. The maximum time difference between laboratory tests and CTA was 12 hours and 32 minutes, with an average time of 3 hours and 13 minutes \pm 0.12 minutes.

CT TECHNIQUE AND INTERPRETATION

The CTA protocol for an AMI at our institution includes an initial, unenhanced phase, arterial phase (performed 40 seconds after injection with a contrast agent) and a portal phase (performed 80 seconds after injection). The iodine contrast material used at our institution is Iohexol 350 mg/ml up to 2 ml/kg.

All CTA tests were performed on one of three CT devices: Philips Brilliance 256 (Philips, the Netherlands), Philips Brilliance 64, and GE Discovery 64 (GE, USA). All CT scans were reviewed by board-certified radiologists.

MACHINE LEARNING MODELS

We compared two ML classifiers for predicting mortality in the non-AMI population: random forest [10] and XGBoost [11]. The algorithms were programmed on Python (Version 3.6) utilizing the Sckit-learn and XGBoost open-source libraries.

- **Random forest algorithm** is a successful classification and regression algorithm. The model ensembles multiple randomized decision trees and aggregates their predictions by averaging [12].
- **XGBoost algorithm** implements the gradient boosting decision tree algorithm. In this algorithm new decision trees are added to correct the errors made by existing trees. This algorithm is widely used by data scientists to achieve state-of-the-art results on many ML challenges [11].

We used an increasing order of magnitude of trees (10, 100, 1,000, 10,000) to evaluate the area under the curve (AUC) and accuracy of each model. We repeated the experiment 100 times for each order of magnitude of trees. A randomized 80/20 training/testing split was used for each experiment.

Feature importance is a benefit of using both random forest and XGBoost decision trees models. As the models are being constructed, it is relatively straightforward to calculate importance scores for each variable that is used in the models. Importance is a score that indicates how valuable each variable was in the construction of the decision trees within the models. The more a variable is used, the higher its relative importance [13]. To evaluate the important variables in the current dataset, we averaged the importance scores of 100 XGBoost models with the optimal number of trees.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA). Continuous variables are reported as the mean \pm standard deviation (SD) and categorical variables are reported as percentages. A two-tailed *P*-value < 0.05 was considered statistically significant. All analyses were performed for the non-AMI group.

The associations between past medical history pathologies and mortality were evaluated (chi-square test) and odds ratios were calculated.

Student's *t*-test was used to examine the relationship between mortality and the following laboratory findings: serum lactate, pH, hemoglobin, white blood cells (WBC), C-reactive protein (CRP), creatinine, lactate dehydrogenase (LDH). The calculations were performed for the entire study population and separately for each referring unit.

To assess the diagnostic ability of laboratory tests and past medical diagnoses to predict mortality, ROC curve was constructed, and AUCs were computed for the entire study population and separately for each referring unit. We compared between the top mean AUCs and accuracies of the random forest and XGBoost models using Student's *t*-test.

RESULTS

DEMOGRAPHIC DATA AND FINAL DIAGNOSES

After exclusion of 73 patients, 325 patients were included in the study. All patients were initially suspected of having had a mesenteric event but eventually were diagnosed with a different medical condition. Table 1 presents the demographic and clinical data of the study cohort. The mean age was 71 ± 16 years. Moreover, the leading underlying conditions in the medical history of each patient were ischemic heart disease (IHD), diabetes mellitus (DM), and paroxysmal atrial fibrillation (PAF). Most of the patients were referred to the CTA exam from the department of internal medicine (41%) and the emergency department (ED, 37%). The overall mortality rate was 24%. Of 325 patients, 108 (33%) were finally diagnosed with a gastrointestinal condition which included infections such as enteritis and colitis, upper or

Table 1. Demographic and clinical characteristics of study population

Number of patients	325	100%
Age, years (mean \pm standard deviation)	71.08 \pm 16.06	
Sex		
Female	171	52.615
Male	154	47.385
Medical history		
Ischemic heart disease	115	35.385
Paroxysmal atrial fibrillation	96	29.538
Chronic atrial fibrillation	29	8.923
Diabetes mellitus	109	33.538
Chronic obstructive pulmonary disease	38	11.692
Chronic kidney disease	52	16.000
Smoker	35	10.769
Referral unit		
Emergency department	123	37.846
Intensive care unit	23	7.07
Internal medicine	134	41.23
Surgery	45	13.846
Final diagnoses		
Gastrointestinal*	108	33.23
Biliary pancreatic**	87	26.769
Miscellaneous $\diamond\diamond$	32	9.846
Infectious disease###	25	7.692
Oncology***	24	7.384
Pulmonary#	19	5.846
Cardiovascular \diamond	17	5.23
Urology##	13	4

*Gastrointestinal diagnoses include bowel obstructions, upper and lower gastrointestinal bleeding, intussusception, hiatal hernia, enterocutaneous fistula, enteritis, and colitis

**Biliary-pancreatic diagnoses include cholecystitis, cholangitis, biliary stones, pancreatitis and pancreatic cysts

***Oncology diagnoses include solid and hematologic tumors

#Pulmonary diagnoses include pneumonia, pulmonary abscesses, pulmonary edema and hemorrhage, COPD exacerbations

##Urologic diagnoses include urosepsis, urinary tract infections, and renal colic

###Infectious diseases not otherwise specified include endocarditis, osteomyelitis, discitis, sepsis, and septic shock

\diamond Cardiovascular diagnoses include congestive heart failure, cardiac tamponade, cardiac arrest, cardiogenic shock and non-ST-elevation myocardial infarction.

$\diamond\diamond$ Miscellaneous diagnoses include post-surgical complications, retroperitoneal and psoas hematoma, diabetic ketoacidosis, splenic infarcts and pelvic fractures

lower gastrointestinal bleeding, and bowel obstruction. The second most common diagnoses were related to the biliary system and pancreas and included cholecystitis and pancreatitis. All other final diagnoses are listed in Table 1.

MORTALITY RATE BY MEDICAL HISTORY

Table 2A summarizes the relationship between past medical history and mortality in the non-AMI group. Only chronic kidney disease (CKD) was found to be a significant prognostic factor for mortality, with an odds ratio of 2.2.

LABORATORY FINDINGS AS A PROGNOSTIC FACTOR

LDH was found to be significant risk factor for mortality in the entire cohort, with AUC 0.703, and for all referral units except the ICU the AUC ranged from 0.748 to 0.788 [Table 2B].

In the internal medicine department, high levels of LDH, lactate, CRP, and creatine had AUC above 0.7 [Table 2B]. In the surgery departments and ED patients both LDH and WBC had AUC above 0.7. The only lab test with prognostic significance in the ICU was pH with AUC 0.792 [Table 2B].

MACHINE LEARNING MODELS

Table 3 presents the AUCs of the two models for an increasing order of magnitude number of trees. The top mean XGBoost AUC and accuracy were achieved with a 1000 trees model (AUC 0.823, accuracy 0.792). The top mean AUC and accuracy of the random forest model were achieved with a 10,000 trees model (AUC 0.800, accuracy 0.787). Only the AUC was found to be significantly different between the XGBoost and random forest models ($P = 0.001$ for AUC, $P = 0.875$ for accuracy).

Figure 1 presents an analysis of features importance for the XGBoost algorithm. The top three most important features for the model were WBC, LDH, and patient age.

DISCUSSION

We examined the relationship between clinical diagnoses and laboratory findings and mortality rate in patients with a suspected AMI who were diagnosed with other medical condition.

While a mesenteric event is an infrequent medical diagnosis, patients [2], most patients with suspected AMI eventually are diagnosed and treated for other conditions [2,14].

In our study, the overall mortality rate in the non-AMI group was 24.6%. Although lower than the 70% mortality rate of AMI patients, this rate is still substantial and represent the complicated population with suspected AMI. Furthermore, most of the patients with a suspected AMI are elderly, with a mean age of 75 years [14]. In our study, the mean age was 71 years.

Most of the patients in our study had a final diagnosis of either a gastrointestinal condition such as bowel obstruction, hernia, or bleeding or pancreaticobiliary diseases such as cholecystitis, cholelithiasis, pancreatitis, and cystic lesions of the pancreas.

Table 2. Mortality rate

[A] Mortality rate according to medical history

Medical history	Number of patients	Mortality	%	P-value	Odds ratio
Ischemic heart disease	115	32	27.826	0.334	1.29
Paroxysmal atrial fibrillation	96	21	21.875	0.446	0.803
Chronic atrial fibrillation	29	8	27.586	0.705	1.179
Diabetes mellitus	111	28	25.225	0.873	1.044
Chronic obstructive pulmonary disease	39	10	25.641	0.884	1.059
Chronic kidney disease	52	20	38.462	0.012	2.203
Smoker	35	6	17.143	0.269	0.599

Bold signifies significance

[B] Mortality rate according to lab tests results by referral unit

Lab tests	Entire cohort	Internal medicine	Surgery	Intensive care unit	Emergency department
Lactate					
AUC	0.652	0.766	0.639	0.587	0.626
P-value	< 0.001	< 0.0001	0.218	0.47	0.066
pH					
AUC	0.596	0.533	0.609	0.792	0.684
P-value	0.01	0.588	0.339	0.015	0.005
Hemoglobin					
AUC	0.620	0.608	0.691	0.514	0.423
P-value	0.001	0.055	0.093	0.908	0.241
White blood cells					
AUC	0.673	0.658	0.789	0.382	0.717
P-value	< 0.001	0.006	0.011	0.326	0.001
C-reactive protein					
AUC	0.581	0.735	0.563	0.48	0.537
P-value	0.031	< 0.0001	0.794	0.88	0.567
Creatinine					
AUC	0.692	0.714	0.671	0.639	0.648
P-value	< 0.001	< 0.005	0.132	0.248	0.024
Lactate dehydrogenase					
AUC	0.703	0.761	0.788	0.667	0.748
P-value	< 0.001	< 0.0001	0.012	0.166	0.001

AUC = area under the curve

Bold signifies significance

This finding is in concordance with other studies that concluded that clinical symptoms and laboratory findings are insufficient for the diagnosis of AMI and supported the common practice of using CT scans to diagnose the alternative pathologies [7].

The highest mortality rate was among patients in the ICU (47.8%). This rate represents the severity and complicated med-

ical problems, which characterize patients admitted to the ICU department [15].

While mortality rate was highest in the ICU, most of the laboratory tests were not significant enough to be an independent factor for mortality. This finding is plausible since evaluation of severity and prognosis among ICU patients requires a combina-

Table 3. Decision tree based on the study data

	Number of trees			
	10	100	1000	10,000
Random forest				
Mean AUC	0.764 ± 0.061	0.790 ± 0.064	0.798 ± 0.063	0.800 ± 0.060
Mean accuracy	0.766 ± 0.036	0.780 ± 0.043	0.784 ± 0.042	0.787 ± 0.04
XGBoost				
Mean AUC	0.780 ± 0.059	0.812 ± 0.047	0.823 ± 0.050	0.822 ± 0.045
Mean accuracy	0.778 ± 0.059	0.791 ± 0.047	0.792 ± 0.050	0.788 ± 0.045

AUC = area under the curve

tion of multiple physiologic variables [15,16].

In accordance with other studies, we found CKD to be a risk factor for mortality. Like other studies [17], which concluded that as kidney function decreases, mortality rates increase, we found CKD to be an independent factor for mortality with an odds ratio of 2.2.

For the various hospital departments, different laboratory values were found to have prognostic significance. This difference may reflect the heterogeneity of this group of patients. Interestingly, for the entire cohort, LDH was found to be the laboratory test with the highest prediction of mortality. LDH correlates with poor prognosis since it is a cellular enzyme that increases due to tissue break-down. Because of that, LDH is found in many disease states such as infection, cancer, and hemolysis. Therefore, high levels of LDH relate to a low survival rate, especially in oncological patients with both solid and hematological tumors [18,19].

One of the goals of our study was to assess the ability of ML algorithms in evaluating prognosis in our study population. According to the analysis, the highest AUC demonstrated in 10,000 trees. From each decision tree the three cardinal variables were patient's age, white blood cells count, and LDH. The results are important since LDH, WBC, and patient's age are common variables in electronic health records and can be used in the future as attributes in machine learning programs that will help to evaluate rapidly and accurately patients with high risk for mortality, even after the exclusion of mesenteric event [8,13].

It is important to mention that our retrospective study had several limitations. First, this study represented the experience of a single medical institution. Second, the population in this study was heterogeneous with different characteristics such as medical background and socioeconomic status. Moreover, because this study combined patients from different medical departments (internal medicine, surgery, ICU, and ED), the primary evaluation was conducted by different doctors, which could lead to selection bias.

CONCLUSIONS

Patients with suspected AMI but a different final diagnosis have a 25% mortality rate. A past medical history of CKD and elevated LDH were found to be associated with increased mortality in this group. A deep learning model achieved higher accuracy for predicting mortality than discrete variables.

Correspondence

Dr. N. Nachmias-Peiser

Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

Fax: (972-3) 535-7315

email: noy.na87@gmail.com

References

1. Singh M, Long B, Koyfman A. Mesenteric ischemia: a deadly miss. *Emerg Med Clin North Am* 2017; 35 (4): 879-88.
2. Menke J. Diagnostic accuracy of multidetector CT in acute mesenteric ischemia: systematic review and meta-analysis. *Radiology* 2010; 256 (1): 93-101.
3. Huang HH, Chang YC, Yen DH, Kao WF, Chen JD, Wang LM, Huang CI, Lee CH. Clinical factors and outcomes in patients with acute mesenteric ischemia in the emergency department. *J Chin Med Assoc* 2005; 68 (7): 299-306.
4. Lange H, Jäkel R. Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. *Eur J Surg* 1994; 160 (6-7): 381-4.
5. Lange H, Toivola A. Varningssignal vid akuta magåkommor. Laktat bästa markören vid mesenterieell ischemi [Warning signals in acute abdominal disorders. Lactate is the best marker of mesenteric ischemia]. *Lakartidningen* 1997; 94 (20): 1893-6. [Swedish].
6. Demir IE, Ceyhan GO, Friess H. Beyond lactate: is there a role for serum lactate measurement in diagnosing acute mesenteric ischemia? *Dig Surg* 2012; 29 (3): 226-35.
7. Cudnik MT, Darbha S, Jones J, Macedo J, Stockton SW, Hiestand BC. The diagnosis of acute mesenteric ischemia: A systematic review and meta-analysis. *Acad Emerg Med* 2013; 20 (11): 1087-100.
8. Steele AJ, Denaxas SC, Shah AD, Hemingway H, Luscombe NM. Machine learning models in electronic health records can outperform conventional survival models for predicting patient mortality in coronary artery disease. *PLoS One* 2018; 13 (8): e0202344.
9. Kogan S, Zeng Q, Ash N, Greenes RA. Problems and challenges in patient information retrieval: a descriptive study. *Proc AMIA Symp* 2001; 329-33.
10. Breiman, L. Random forests. *Machine Learning* 2001; 45 (1): 5-32.

11. Burnaev E, Koptelov I, Novikov G, Khanipov T. Automatic construction of a recurrent neural network based classifier for vehicle passage detection. In Ninth International Conference on Machine Vision (ICMV 2016) Vol. 10341; 2017: 7-12. SPIE.
12. Biau G, Scornet E. A random forest guided tour. *Test* 2016; 25 (2): 197-227.
13. Obermeyer Z, Lee TH. Lost in Thought - The Limits of the Human Mind and the Future of Medicine. *N Engl J Med* 2017; 377 (13): 1209-11.
14. Kärkkäinen JM, Acosta S. Acute mesenteric ischemia (part I) - Incidence, etiologies, and how to improve early diagnosis. *Best Pract Res Clin Gastroenterol* 2017; 31 (1): 15-25.
15. Dijkema LM, Dieperink W, van Meurs M, Zijlstra JG. Preventable mortality evaluation in the ICU. *Critical Care* 2012; 16 (2): 309.
16. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985 ;13 (10): 818-29.
17. Tonelli M, Wiebe N, Culleton B. et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006; 17: 2034-47
18. Wulaningsih W, Holmberg L, Garmo H, et al. Serum lactate dehydrogenase and survival following cancer diagnosis. *Br J Cancer* 2015; 113: 1389-96.
19. Erez A., Shental O., Tchebner J.Z. Diagnostic and prognostic value of very high serum lactate dehydrogenase in admitted medical patients. *IMAJ* 2014; 16 (7): 439-43.

Capsule

T cells in vaccine immunity

Whether a person has protective immunity derived from a vaccine is usually measured in terms of neutralizing antibody responses. SARS-CoV-2 variants have mutations that reduce neutralization by antibodies, which has increased breakthrough infections in vaccinated people. However, these infections have not proportionally increased hospitalization and deaths, indicating that antibodies are not the whole story. In a perspective, **Wherry** and **Barouch** discussed the emerging role of T cell immunity

in preventing severe COVID-19, even when it is caused by antibody-escape variants. Measuring T cell responses to vaccines will improve our understanding of their role in immune protection, especially in the long term after antibody waning. This work should also lead to optimized immune protection strategies, including the development of updated COVID-19 or pan-beta-coronavirus vaccines.

Science 2022; 377: 821

Eitan Israeli

Capsule

Uncovering a contributor to Parkinson's disease

Genome-wide association studies (GWAS) have uncovered nearly 100 loci that contribute to risk for Parkinson's disease (PD), which affects an estimated 6 million people worldwide. However, target genes and biological mechanisms associated with these loci remain largely unexplored. **Diaz-Ortiz** and colleagues examined a PD GWAS risk locus on chromosome 7, linking it to the transmembrane protein Glycoprotein Nonmetastatic

Melanoma Protein B (GPNMB). GPNMB was found to interact with alpha-synuclein (aSyn), the key protein that forms the pathological inclusions that characterize PD. In cells, GPNMB was both necessary and sufficient for the uptake of fibrillar forms of aSyn and the subsequent development of aSyn pathology.

Science 2022; 377: 833

Eitan Israeli

Capsule

STAND against viral invaders

The innate immune systems of animals, plants, and fungi universally use nucleotide binding oligomerization domain-like receptors (NLRs) of the STAND superfamily to detect molecular patterns common to pathogens. **Gao** et al. showed that NLR-based immune pattern recognition is also prevalent in bacteria and archaea, something that was not known before. In particular, the authors characterized four families of NLR-like genes, finding that they are specific sensors for two highly conserved

bacteriophage proteins. When binding to the target, these NLRs activate diverse effector domains, including nucleases, to prevent phage propagation. These findings demonstrate that pattern recognition of pathogen-specific proteins is a common mechanism of immunity across all domains of life.

Science 2022; 377: 726

Eitan Israeli