Absence of Stress Hyperglycemia Indicates the Most Severe Form of Blunt Liver Trauma (AAST V) – A Register Analysis

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Research

Abstract

Background: Stress hyperglycemia is common in trauma patients. Increasing injury severity and hemorrhage is known to trigger hepatic gluconeogenesis and glycogenolysis and also peripheral and hepatic insulin resistance. Consequently, we expect glucose levels to rise with injury severity in liver, kidney and spleen injuries. In contrast, we hypothesized that in the most severe form of blunt liver injury, stress hyperglycemia may be absent despite critical injury and hemorrhage.

Methods: All patients with documented liver, kidney or spleen injuries, treated at a single, university hospital in Austria between 2000 and 2020 were charted in a register. Besides demographic, laboratory, radiological, surgical and other data were analyzed.

Results: A total of 772 patients were included. In liver (n=456), spleen (n=375) and kidney (n=152) trauma, an increasing injury severity past moderate to severe (AAST III-IV) was associated with a concomitant rise in blood glucose levels independent of the affected organ. While this stress induced hyperglycemia was even more pronounced in the most severe forms (AAST V) of spleen (median 10.7 mmol/L, p<0.0001) and kidney injuries (median 10.6 mmol/L, p=0.004), it was absent in AAST V liver injuries, where median blood glucose level even fell (5.6 mmol/L, p<0.0001).

Conclusions: Absence of stress hyperglycemia is a sign of most severe liver injury (AAST V) and should prompt fundamental diagnostic and therapeutic procedures. Blood glucose should be considered as an additional diagnostic criterion in liver injury.

Introduction

Stress hyperglycemia is common in trauma patients and critical illness upon hospital admission and is often associated with worse outcome [1–4]. Hemorrhage aggravates this stress hyperglycemia significantly [5, 6]. Caused by hepatic gluconeogenesis, glycogenolysis and hepatic as well as peripheral insulin resistance its' probable pathophysiological purpose is to shift energy substrates to vital organs, initial immune defense, and repair mechanisms [7–12] and can therefore be seen as a survival response.

Consequently, according to literature, hypoglycemia is an rare finding in trauma patients upon hospital admission and mainly triggered by non-traumatic causes such as anti-diabetic drug overdose, alcohol intoxication or chronic liver disease [13,14].

The injury severity of parenchymatous organs like liver, kidney or spleen is often radiologically categorized according to the classification of the American Association for the Surgery of Trauma, AAST [15, 16]. In doing so, the extent of lacerations, contusions or hematomas must be exactly measured. However, specifying proportions of parenchymal disruption of one or both hepatic lobes to distinguish between liver injury AAST IV and V may be very challenging.

It was hypothesized that, in parallel with injury severity and extent of hemorrhage, in hepatic, renal or splenic injuries, blood glucose levels should increase and therefore lead to significant stress hyperglycemia. However, it was also hypothesized that in case of most severe liver injuries (AAST V), defined by major devascularization (inflow or outflow) and/or parenchymal disruption of more than 75% of one hepatic lobe, hepatic gluconeogenesis and glycogenolysis may become insufficient, consequently leading to absence of stress hyperglycemia. This may be a leading diagnostic mark.

Methods

The study was reviewed and approved by the Ethic Committee of the Medical University of Innsbruck (EK 1394/2020) and written informed consent was waived due to the observational character of the study.

Aim: All trauma patients with suspected blunt hepatic, splenic or renal injury, treated at the Medical University Hospital of Innsbruck between January 1, 2000 and August 31, 2020 (inclusion criteria) were analyzed regarding stress hyperglycemia and relevant aim and outcome factors.

Design and setting: This single center analysis of detailed medical information on hepatic, splenic and renal injuries was obtained by searching the local hospital information system (Krankenhausinformationssystem i.s.h.med PowerChart by Cerner Österreich GmbH, Vienna, Austria), which is prospectively maintained and auditable. A pre-existing register – developed for the analysis of treatment strategies and associated outcomes in blunt liver, spleen and kidney injuries [17,18] over a 17-year period (2000-2016) – was expanded up to 2020, extended by blood glucose values upon hospital admission and re-analyzed with different inclusion and exclusion criteria (Figure 1).

Patients: Besides the above-mentioned inclusion criteria, the following exclusion criteria were applied: missing blood glucose levels within the first hour following hospital admission, insufficient documentation of radiologic findings or laboratory analyses regarding the scientific question, admission more than 12 hours beyond trauma, death at arrival and hemorrhages due to innate malformations (Figure 1).

Patients transferred from district hospitals to our level 1 trauma center after receiving diagnostics only and within the 12 hours timeframe were also included. Patients with diabetic mellitus were included. All patients received either selective abdominal/thoracic/cranial or whole body dual or triple phase computed tomography (CT) scans. CT images were re-evaluated regarding injury grading by two trained radiologists using our picture archiving and communication system (AGFA IMPAX; AGFA Health Care, Greenville, SC).

Processes: The patients' demographic data as well as all radiology, clinical and necessary laboratory findings were charted. Hepatic, splenic and renal injuries were graded by the 2018 revision of the American Association for the Surgery of Trauma (AAST) classification system [15,16]. In addition, all injuries including co-injuries were classified according to the Abbreviated Injury Scale (AIS, version 2005,

update 2008) and allocated to the appropriate organ system [19]. The injury severity score, ISS, was calculated as described in the original publication [20].

Statistical analysis: Injury scoring took place on the basis of the AAST classification for blunt liver, spleen or kidney trauma in all patients suffering from injuries of at least one of these organs and, additionally, in patients suffering from injuries of one of these organs but excluding severe co-injuries classified as AIS 4-6 in any other organ or organ system. This was done to demonstrate independent effects of particular organ injuries on blood glucose levels.

Descriptive statistical analysis was performed reporting proportions (%) and medians with range due to non-normal distribution of data. Group differences were analyzed by Mann-Whitney *U* test. Due to small subgroups, two-tailed p values less than 0.05 were accepted as significance level throughout the study. Data analysis was performed with SPSS 26.0 (IBM Corporation, Armonk, NY, USA).

Results

During the study period, 879 patients presented with suspected hepatic, splenic or renal injury to our level 1 trauma center were assessed for eligibility. Exerting inclusion and exclusion criteria, 772 patients, comprising 456 liver, 375 spleen and 152 kidney injuries were finally included in the study; 189 patients had more than one organ injured. (Figure 1) Median age was 29 years (1 - 89), 238 patients (31%) were female. During hospitalization, 26 patients (3.4%) deceased. (Table 1)

We found 456 patients with liver injuries; they were classified as 80 patients with AAST I, 125 patients with AAST II, 176 patients with AAST III, 64 patients with AAST IV, and 11 patients with AAST V. Initial blood glucose levels increased highly significant from 6.58 mmol/L (4.50 - 24.64 mmol/L) in patients with AAST I injuries to 8.60 mmol/L (5.55 - 27.19 mmol/L) in patients with AAST IV injuries (p<0.0001). In patients with AAST V injuries, median initial blood glucose dropped to 5.77 mmol/L (2.33 - 7.83 mmol/L), which was significantly lower than in AAST I (p=0.01) and IV injuries (p<0.0001). (Figure 2a)

Excluding patients with diabetes mellitus (n=6) resulted in very similar results (Figure 2b). Excluding patients with severe co-injuries (AIS 4-6, n=200) (Figure 2c) and, additionally, patients with diabetes mellitus (Figure 2d) demonstrated more clearly the effects of injury severity on blood glucose levels. Median blood glucose levels rose highly significant from 6.08 mmol/l (4.50 – 7.77 mmol/L) in patients with AAST I to 8.91 mmol/L (5.55 - 27.19 mmol/L) in patients with AAST IV injuries. In patients with AAST V injuries, stress hyperglycemia was absent. Their blood glucose levels did not rise (5.58 mmol/L (3.83 - 6.94 mmol/L)). (Figure 2d, to AAST I p=0.19, to AAST IV p=0.0006) despite higher injury severity and blood losses.

Of 11 patients with AAST V injuries, only two patients deceased; one due to uncontrollable bleeding of the liver and partial avulsion of the inferior vena cava, one due to uncontrollable bleeding of the liver and multiple fractures to the pelvis. Of the nine surviving AAST V-patients, merely one required glucose administration to maintain physiological blood glucose levels within the following days after admission.

This was a 13-year-old child, also in need of repeated administration of coagulation factors. In all other patients, blood glucose levels improved over time without additional glucose administration.

We found 375 patients with spleen injuries; they were graded as 62 patients with AAST I, 83 patients with AAST II, 142 patients with AAST III, 59 patients with AAST IV, and 29 patients with AAST V injuries. Initial blood glucose levels rose highly significant from 7.13 mmol/L (4.83 - 24.81 mmol/L) in patients with AAST I to 10.71 mmol/L (5.61 - 18.48 mmol/L) in patients with AAST V injuries. Initial blood glucose in patients with AAST V injuries rose comparably, there was no drop (Figure 3a). Excluding patients with diabetes mellitus (n=6) resulted in very similar results (Figure 3b). Excluding patients with severe co-injuries (AIS 4-6, n=163) (Figure 3c) and, additionally, patients with diabetes mellitus (Figure 3d) eliminated outliers and demonstrated more clearly that initial blood glucose rose continuously with rising injury severity and blood losses. Blood glucose in patients with AAST IV and AAST V injuries of the spleen differed highly significantly from patients with AAST I injuries. (Figures 3c and d)

Kidney injuries were far more seldom; overall, 152 patients were analyzed; they were graded as 21 patients with AAST I, 36 patients with AAST II, 41 patients with AAST III, 48 patients with AAST IV, and 6 patients with AAST V injuries. Initial blood glucose levels rose highly significant from 6.49 mmol/L (5.27 - 11.16 mmol/L) in patients with AAST I to 9.60 mmol/L (8.88 - 18.48 mmol/L) in patients with AAST V injuries. There was no drop of median initial blood glucose in patients with AAST V injuries (Figure 4a). Excluding patients with diabetes mellitus (n=3) resulted in similar results (Figure 4b). Excluding patients with severe co-injuries (AIS 4-6, n=73) (Figure 4c) and, additionally, patients with diabetes mellitus (Figure 4d) demonstrated – due to less exceptions and outliers - more clearly that initial blood glucose rose continuously with rising injury severity of the kidneys and blood losses. Blood glucose in patients with AAST IV and AAST V injuries of the kidney differed highly significantly from patients with AAST I injuries. (Figures 4c and d)

Discussion

The results of this retrospective, single center trial demonstrated that stress hyperglycemia develops in parallel to injury severity in patients with blunt spleen or kidney trauma. While consistent results were obtained for blood glucose levels in blunt liver injuries up to AAST IV, stress hyperglycemia was completely absent in the most severe cases (AAST V).

Over the last two decades, a vast number of publications have demonstrated the fundamental role of stress hyperglycemia in critical injury [1–4] and diverse critical conditions [21–24]. Up to date, there has been no consistency in defining blood glucose levels, wherefore this trial resigns from specifying any threshold values for stress hyperglycemia.

Pathophysiological source of stress hyperglycemia seems to be a rampant hepatic glycogenolysis [9] but also gluconeogenesis from lactate, free fatty acids, and alanine [7, 8, 25]. Decoupling of both processes from physiological feedback mechanisms controlling glucose homeostasis is thought to be caused by hepatic [11, 12, 26] and intensified by muscular insulin resistance [27]. Hemorrhage is a potential

multiplier of trauma associated stress hyperglycemia [5, 6], wherefore injuries of parenchymatous organs like the liver, spleen or kidney are capable of triggering stress hyperglycemia amongst others due to blood loss associated with increasing injury severity. With regards to the corresponding definitions of AAST classified injuries, active bleeding is included in AAST ≥ III injuries of the liver and kidney and AAST ≥ IV injuries of the spleen [15, 16]. AAST V injuries of the liver are furthermore defined as major juxtahepatic venous injury (vena cava, central major hepatic veins) or lacerations resulting in parenchymal disruption of more than 75% of one hepatic lobe [15, 16]. Assuming the liver is the primary origin of stress hyperglycemia, it seems clear that such destroying liver injuries, partially even resulting in devascularization (inflow or outflow) can impede hepatic glucose liberation provoked by trauma or hemorrhage, as demonstrated in this trial for the first time.

Surprisingly, besides one child, none of the surviving adults with AAST V hepatic injuries was in need of any additional glucose administration to maintain blood glucose levels within physiological range. In patients with initially low or very low (hypoglycemic) blood glucose levels, blood glucose levels recovered spontaneously to typically increased blood glucose levels following severe trauma. Apparently, the residual hepatic tissue was able to cover physiologic needs, but needed several hours to adopt. Nevertheless, the relatively low blood glucose levels were of high diagnostic importance.

In the literature, the kidneys are also seen as relevant source of blood glucose production (up to 40% of circulating blood glucose) following epinephrine stimulation [28, 29]. Although body's own catecholamines should be relevantly increased during severe hemorrhage as detected in AAST V liver injuries in this study, blood glucose dropped in these patients and was not increased by renal glucose delivery. Possible attempts of explanation may include insufficient renal perfusion during hemorrhagic shock or mere lack of time or substances (glutamine, glycerol, lactate) for sufficient renal glucose production. In particular, circulating glutamine is mainly provided by the liver and therefore, in case of AAST V injury of the liver, probably lacking.

This study did not differ among adults, children or diabetics. We did not find significant differences between adults and children probably due to the low median age of analyzed patients. Besides observed outliers of high blood glucose levels, patients with diabetes mellitus had no relevant impact on our results. We did not exclude them from analysis as we felt they realistically represent the expectable extent of clinical settings.

Furthermore, we did not analyze lactatemia due to unreliability in initial laboratory results upon hospital admission [6]. Lactatemia is influenced by circulation, production, metabolism and volume resuscitation as well as administration (Ringer's lactate), if applicable. Therefore, initial laboratory results may vary fundamentally not always reflecting severity of injury and hemorrhage, respectively.

In contrast, blood glucose levels upon hospital admission seem to be independent from pre-hospital fluid and volume administration and a reliable, additional diagnostic tool for trauma patients [6] without collinearity to vital or laboratory parameters commonly used upon initial trauma assessment. However, if critically injured patients present with low blood glucose levels, questions should arise: besides most

severe liver injuries, anti-diabetic drug overdose, alcohol abuse, severe hypothermia or any other reason for limited liver function could be causative [13, 30, 31].

Pancreatic injuries were rare in this population. Merely eight patients suffered from concomitant pancreatic injury: five pancreatic contusions treated conservatively and three pancreatic ruptures were in need of surgical intervention. One segment resection, one surgical closure of the rupture and one complete pancreas resection were performed. Severe pancreatic affection was mainly concomitant to liver injuries. Blood glucose differed widely and independent to extent of pancreatic injury from 5.05 to 24.81 mmol/L. Based on the limited number of those affected, the authors could not conclude that pancreatic injuries had relevant impact on initial blood glucose in this patient population.

Pre-hospital vital parameters were not sufficiently documented within the digitalized local hospital information system during the initial decade of the study phase. Therefore, pursued calculation of trauma scores was not possible. Further limitations of this study are the single center and retrospective design as well as the low patient number in certain subgroups.

Nevertheless, this large database of patients with blunt hepatic, splenic, and renal injuries sufficiently demonstrated significant results, especially regarding median blood glucose drop in most severe liver injuries (AAST V). Blood glucose levels should be part of diagnostic calculations, and also be considered in differentiation between severe liver injuries (AAST IV vs. V).

Conclusions

Absence of stress hyperglycemia is a sign of most severe liver injury (AAST V) and should prompt fundamental diagnostic and therapeutic procedures. Blood glucose should be considered as additional diagnostic criterion in liver injury.

Declarations

Ethics approval and consent to participate

Approval for this prospective trial was obtained by the ethics committee of the Medical University of Innsbruck (EK 1394/2020). All data used in this analysis were anonymised and thus the Ethical Committee withdraw the requirement for patients or next of kin to consent to take part in the trial.

Consent for publication

The manuscript does NOT contain any patient's personal data. Therefore, the authors state: "Not applicable in this section".

Availability of data and materials

All data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization: J.K. and S.Sch.; methodology: J.K. and S.St.; validation: J.K, C.R. and S.Sch.; formal analysis: J.K.; investigation and resources: M.F., F.P. and S.St.; radiology data investigation and curation: D.M-H. and E.G.; data curation: J.K. and M.F.; writing—original draft preparation: J.K., M.F. and C.R.; writing—review and editing: all authors; visualization: J.K.; supervision: J.K. and C.R.; project administration: M.F.; All authors have read and agreed to the published version of the manuscript.

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Tables

Table 1: Study population characteristic

	median/number	range/percent
age	29	1-89
female/male	238 / 534	30.8 / 69.2
deceased	26	3.4
hospital length of stay (d)	13	0 – 112
blood glucose (mmol/L) [1]	7.16	2.33 - 27.19 [1]
ISS[2]	21	1 - 75

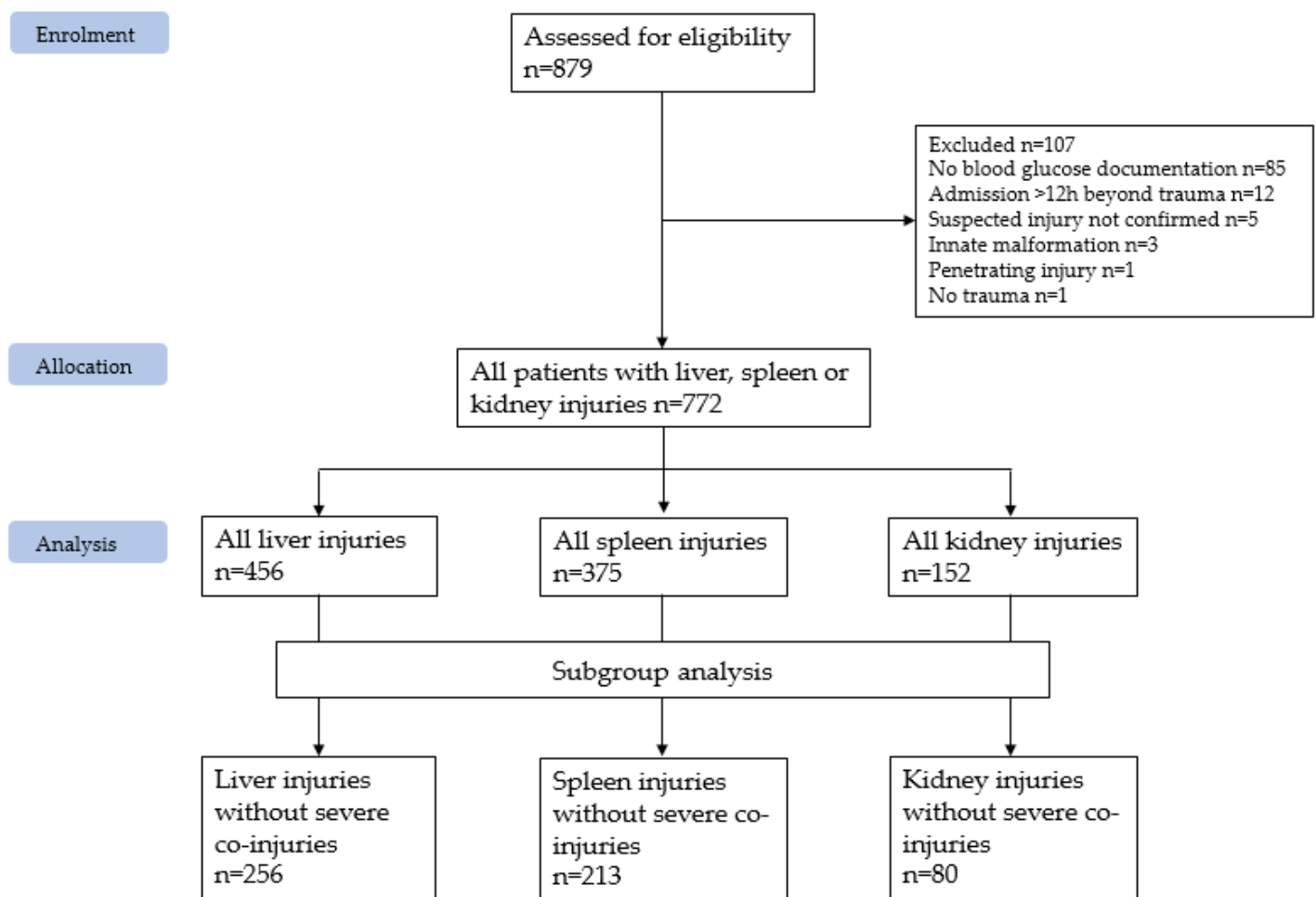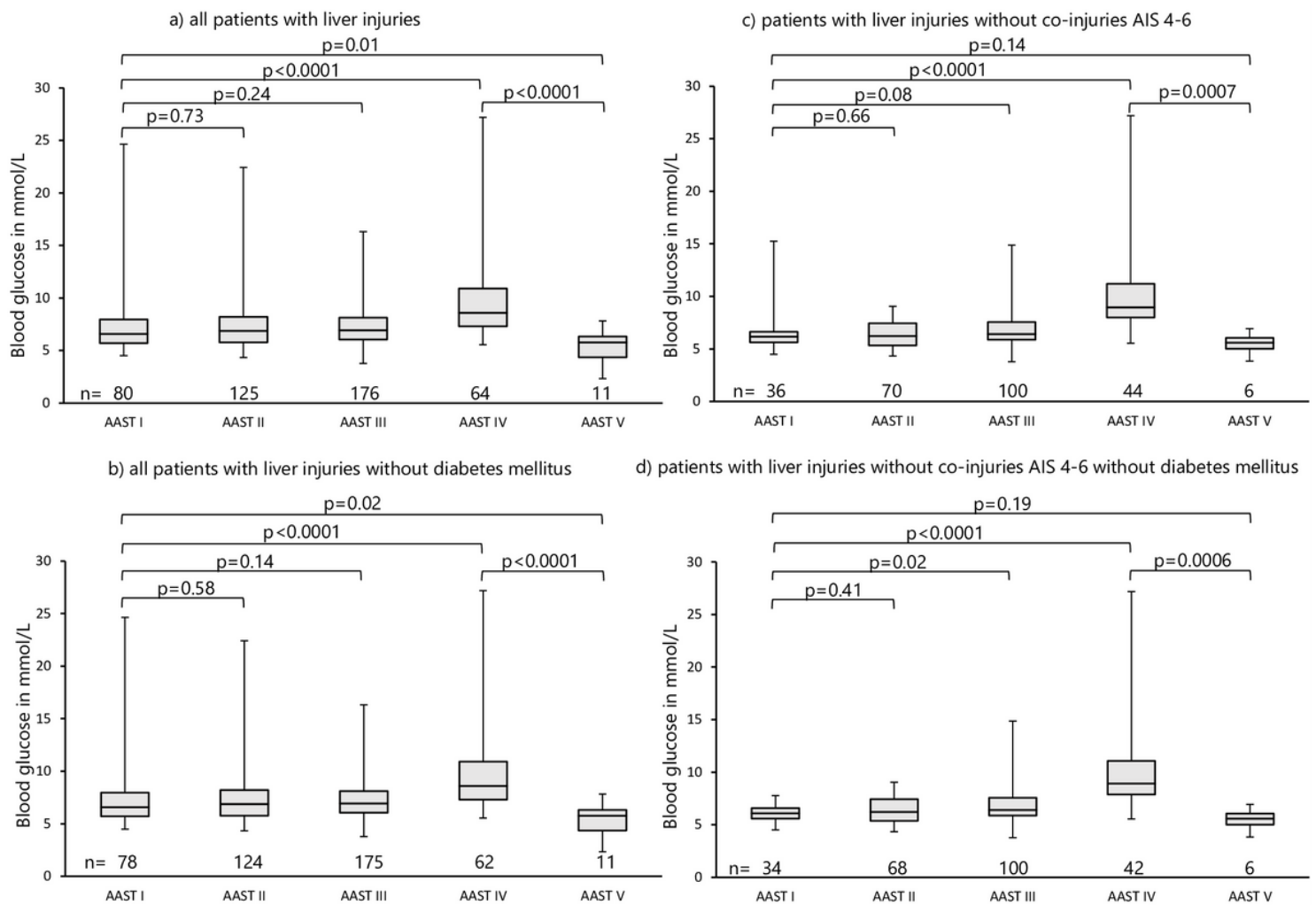[1] measured within first hour following admission; [2] Injury severity score [18]

Figures
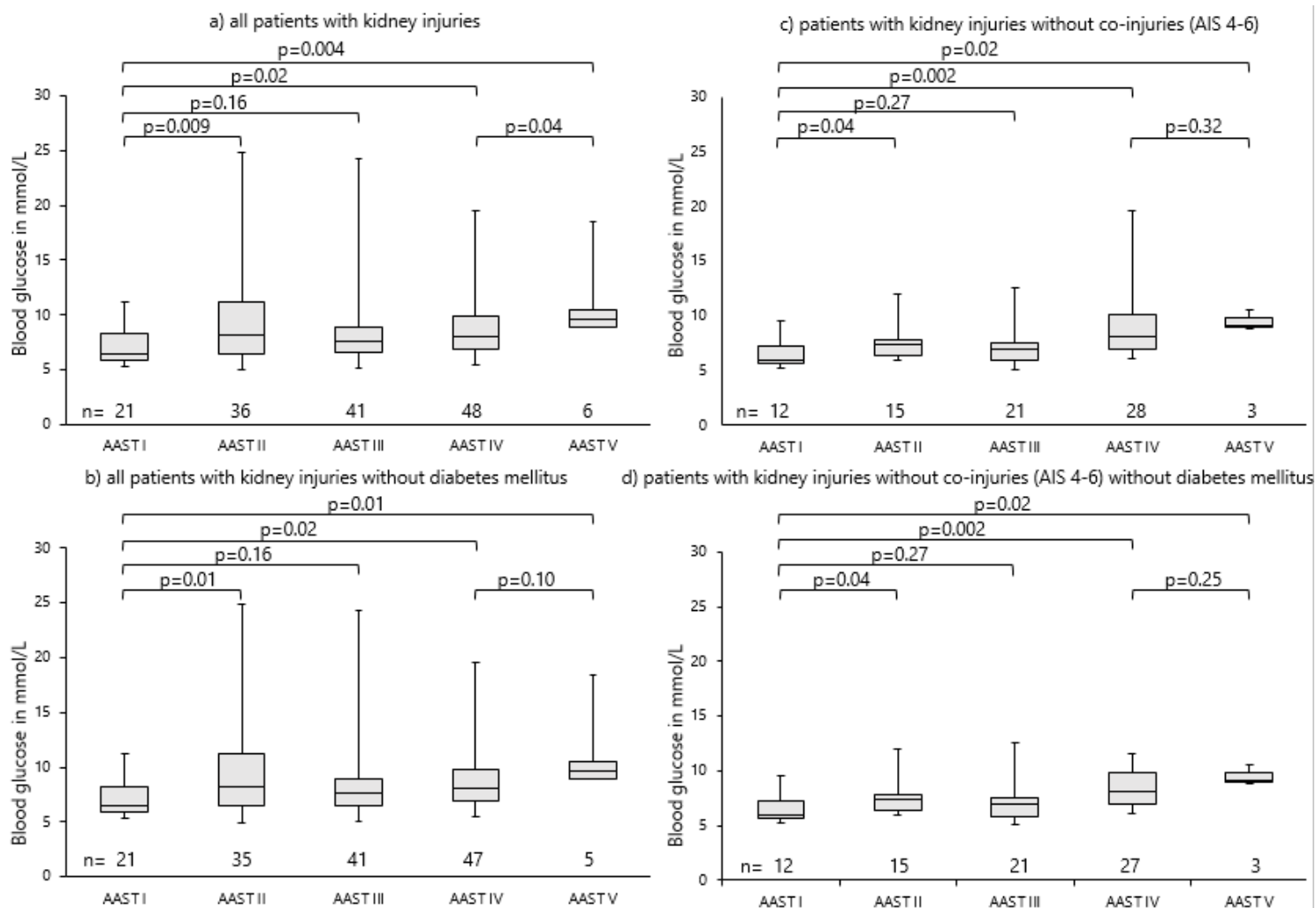

Figure 1

CONSORT flow diagram of patient population

Figure 2

Rising Blood glucose levels in parallel to severity of liver injury. Outliers of very high blood glucose levels in less severe injuries (AAST I-III) were found in patients with diabetic mellitus disease. AAST American Association for the Surgery of Trauma [15,16]
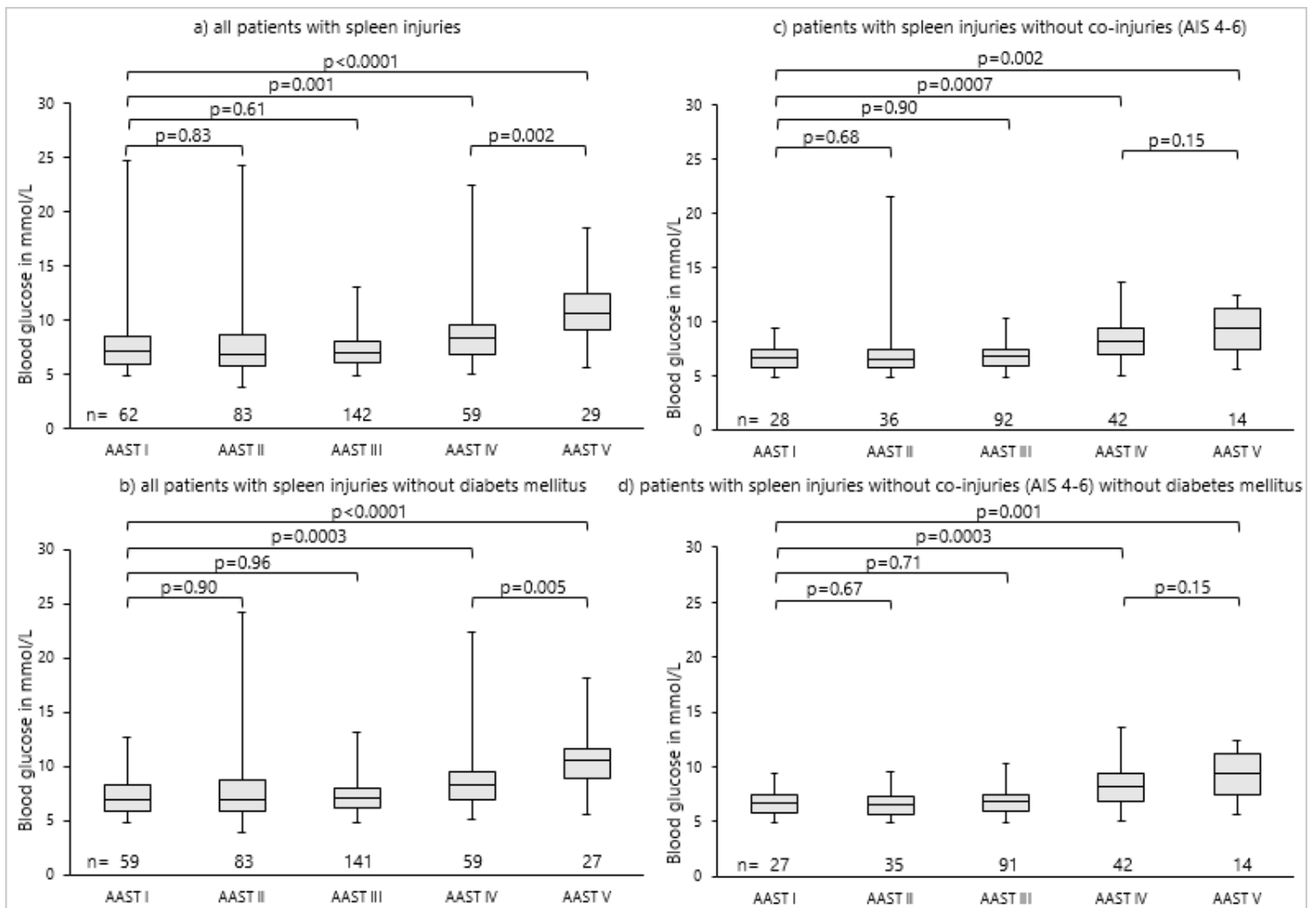
Figure 3

Rising blood glucose levels in parallel to injury severity in splenic injuries. Outliers of very high blood glucose levels in less severe injuries (AAST I-III) were found in patients with diabetic mellitus disease. AAST American Association for the Surgery of Trauma [15,16]

Figure 4

Rising blood glucose levels in parallel to injury severity in renal injuries. Outliers of very high blood glucose levels in less severe injuries (AAST I-III) were found in patients with diabetic mellitus disease. AAST American Association for the Surgery of Trauma [15,16]

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