Medicine®

OPEN

Early diagnosis of hollow viscus injury using intestinal fatty acid–binding protein in blunt trauma patients

Shokei Matsumoto, MD[a,*], Kazuhiko Sekine, MD[b], Hiroyuki Funaoka, PhD[c], Tomohiro Funabiki, MD[a], Masayuki Shimizu, MD[a], Kei Hayashida, MD[a], Mitsuhide Kitano, MD[a]

Abstract

A delay in diagnosing hollow viscus injury (HVI) causes an increase in mortality and morbidity. HVI remains a challenge to diagnose, and there is no specific diagnostic biomarker for HVI. We evaluated the utility of intestinal fatty acid–binding protein (I-FABP) in diagnosing HVI in blunt trauma patients. Within a 5-year period, 93 consecutive patients with clinically suspected HVI at our trauma center were prospectively enrolled. The diagnostic performance of I-FABP for HVI was compared with that of other various parameters (physical, laboratory, and radiographic findings). HVI was diagnosed in 13 patients (14%), and non-HVI was diagnosed in 80 patients (86%). The level of I-FABP was significantly higher in patients with HVI than in those with non-HVI ($P = 0.014$; area under the curve, 0.71). The sensitivity, specificity, positive predictive value, and negative predictive value were 76.9%, 70.0%, 29.4%, and 94.9%, respectively ($P = 0.003$). However, all other biomarkers were not significantly different between the groups. Presence of extraluminal air, bowel wall thickening on computed tomography (CT), and peritonitis signs were significantly higher in patients with HVI ($P < 0.05$). Of 49 patients (52.7%) who had a negative I-FABP and negative peritonitis signs, none developed HVI (sensitivity, 100%; negative predictive value, 100%). This is the first study that demonstrated the diagnostic value of a biomarker for HVI. I-FABP has a higher negative predictive value compared to traditional diagnostic tests. Although the accuracy of I-FABP alone was insufficient, the combination of I-FABP and other findings can enhance diagnostic ability.

Abbreviations: AIS = Abbreviated Injury Score, AMY = amylase, ATLS = Advanced Trauma Life Support, AUC = area under the curve, BIPS = Bowel Injury Prediction Score, CT = computed tomography, EAST = Eastern Association for the Surgery of Trauma, FAST = focused assessment with sonography for trauma, GCS = Glasgow Coma Scale, HGB = hemoglobin, HVI = hollow viscus injury, I-FABP = intestinal fatty acid binding protein, ISS = Injury Severity Score, OR = odds ratio, ROC = receiver operator characteristic, US = ultrasonography, WBC = white blood cell count.

Keywords: blunt abdominal trauma, diagnosis, hollow viscus injury, intestinal fatty acid binding protein

1. Introduction

Delayed diagnosis of hollow viscus injury (HVI) significantly increases mortality and morbidity in blunt trauma patients.[1–3] Although medical technology has improved in recent years, diagnosis management in patients with a suspected HVI has not progressed, and exploratory laparotomy is still the most reliable method for diagnosis. However, a negative or nontherapeutic laparotomy has a high risk of complications.[4,5] HVIs are frequently found in patients who undergo laparotomy for hemostasis of other solid organ injuries, but the chances to directly diagnose HVI via laparotomy are decreasing as nonoperative management is becoming more popular. Radiological computed tomography (CT) and diagnostic peritoneal lavage may be considered useful, but they are costly, invasive, and require significant expertise. These methods all have associated problems, and a simple cost-effective and noninvasive diagnostic tool is needed to ensure prompt diagnosis.

At present, there are no specific biomarkers for diagnosing HVI. Although white blood cell count (WBC) is commonly elevated by physical stress in trauma patients, a persistently elevated WBC may suggest a potential HVI based on observation in the first 24 hours.[6] However, even a diagnostic delay of <8 hours results in a worse prognosis.[1] Many studies have reported the diagnostic value of CT for HVI, but there are few studies on the diagnostic value of biomarkers for HVI. Recently, intestinal fatty acid–binding protein (I-FABP) has been suggested as a new biomarker to diagnose intestinal disease.[7–12] It was also reported to be associated with severe abdominal injuries.[13–16] I-FABP is a small (14–15 kDa), cytosolic, water-soluble protein that comprises up to 2% of the cytoplasmic protein content of the mature enterocyte, and is abundant in bowel mucosa. If the intestinal mucosal tissue is injured, I-FABP is rapidly released into the bloodstream. However, no study has examined the diagnostic

[a] Department of Trauma and Emergency Surgery, Saiseikai Yokohamashi Tobu Hospital, Yokohama, Japan, [b] Department of Emergency Medicine, Saiseikai Central Hospital, Minato-ku, Tokyo, Japan, [c] DS Pharma Biomedical Co., Ltd., Osaka, Japan.

* Correspondence: Shokei Matsumoto, Department of Trauma and Emergency Surgery, Saiseikai Yokohamashi Tobu Hospital, 3–6–1 Shimosueyoshi, Tsurumi-ku, Yokohama-shi, Kanagawa 230–0012, Japan (e-mail: m-shokei@feel.ocn.ne.jp).

value of I-FABP for HVI. We hypothesized that I-FABP adds to the diagnostic arsenal in the setting of blunt abdominal trauma. This study was undertaken to evaluate the utility of I-FABP, sampled at the time of admission, in the early diagnosis of HVI.

2. Methods

This study was approved by the local ethics committee of Saiseikai Yokohamashi Tobu Hospital. The study was conducted at the Emergency and Trauma Center of Saiseikai Yokohamashi Tobu Hospital, a tertiary-care hospital in Yokohama, Japan, from January 2010 to December 2014. All consecutive blunt trauma patients with suspected clinical HVI who underwent abdominal and pelvic CT at our trauma department were prospectively enrolled. Clinical findings suggestive of HVI were at least one of the following: abdominal pain, abdominal distention, a mechanism associated with the abdominal region, and abnormal skin on the abdomen. These conditions were identified by an attending acute care surgeon at an initial evaluation. We excluded patients younger than 18 years, and patients with refractory shock who could not undergo a CT.

2.1. Study design and sample collection

After enrollment, the following items were recorded for each patient: age, sex, vital signs, physical abdominal examinations (tenderness and peritoneal signs), radiologic findings, and routine laboratory test results. Peritoneal signs were defined as rebound tenderness and guarding. After the initial assessment, blood samples were taken to investigate I-FABP and other biomarkers. The diagnostic performance of I-FABP for HVI was compared with that of other parameters, including physical, laboratory, and radiographic findings.

All patients were treated according to the Advanced Trauma Life Support (ATLS) Course guidelines,[17] without interference by the research team. The attending Japanese board-certified surgeon determined the operative indication in a comprehensive manner, taking the CT findings, physical examination results, and laboratory results into consideration. According to the clinical and surgical results, the diagnosis of each patient was retrospectively classified as either HVI or non-HVI.

2.2. Radiographic imaging and evaluation

All ultrasonography (US) examinations were performed using a focused assessment with sonography for trauma (FAST) by Japanese board-certified attending emergency physicians. A US imaging unit (Viamo, Toshiba, Tokyo, Japan) with a 5.0-MHz convex probe was used. All CT scans were performed using 64 multidetector CT scanners (Aquilion CT scanner; Toshiba, Tokyo, Japan) at the initial management. Intravenous contrast medium (iohexol, Omnipaque 300; Daiichi Sankyo, Tokyo, Japan) was used in all patients unless contraindicated. CT images were reviewed retrospectively, with agreement between an attending radiologist and an experienced faculty emergency radiologist. The following CT features were assessed: extraluminal air, free fluid, bowel wall thickening, contrast extravasation, and the presence of solid organ injury. These findings were based on a study by Fakhry et al.[2]

2.3. Laboratory analysis

The I-FABP assay is currently in clinical development and has not yet been used in a clinical setting. For the I-FABP assay, samples were stored at −20°C until analysis. I-FABP was measured at the

DS Pharma Biomedical Center in Osaka, Japan, at a later date. Thus, I-FABP did not impact the decision-making in this study. I-FABP serum levels were quantified using synthetic regional peptides and a recombinant I-FABP assay (Dainippon Sumitomo Pharma; Osaka, Japan). The serum I-FABP level in the healthy volunteers was 1.1 ± 0.9 ng/mL, ranging from 0.1 to 2.0 ng/mL.[18] Other biomarkers were as follows: WBC, hemoglobin (HGB), lactate, and amylase (AMY). All other biomarkers were measured immediately in serum using commercially available assays at Saiseikai Yokohamashi Tobu Hospital. The normal ranges of the markers used in this study were as follows: WBC, 3.50 to 8.50 cells/ $mm^3 \times 1000$; HGB (males), 13.8 to 17.2 g/dL; HGB (females), 12.1 to 15.1 g/dL; lactate, 4 to 16 mg/dL, and AMY, 40 to 126 IU/L.

2.4. Statistical analyses

Analysis was performed using the χ^2 test and the Mann–Whitney U test, as appropriate. To identify the diagnostic value of these biomarkers for HVI, receiver operator characteristic (ROC) curves were constructed, and the area under the curve (AUC) was calculated. The best cutoff points were defined as the maximum sum of sensitivity and specificity. A value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient demographics, characteristics, and outcomes

Ninety-three patients were enrolled during the study period. During this study, a total of 3460 blunt trauma patients attended the emergency department, and 2024 patients underwent abdominal CT (including 1912 patients who underwent whole-body CT). Patient characteristics and outcomes are shown in Table 1. Patients in the sample were a mean of 45 years, and the majority were male (72.0%). The median Injury Severity Score (ISS) and the rate of the abdominal Abbreviated Injury Score

Table 1

Patient characteristics and outcomes with hollow viscus injury and nonhollow viscus injury.

Characteristics	Hollow viscus injury (n = 13)	Non-hollow viscus injury (n = 80)	P
Age	38.0 (32–49)	46.0 (26–58)	0.51
Male sex, % (n)	61.5 (8)	73.8 (59)	0.505
ISS	14.5 (12–25)	17.0 (9–28)	0.988
GCS	15 (11.0–15)	14 (11.8–15)	0.739
Abdominal AIS ≥3, % (n)	100 (13)	24.2 (16)	<0.001
Mechanism of injury			
Motor vehicle accident, % (n)	92.3 (12)	77.5 (62)	0.831
Fall, % (n)	7.7 (1)	17.5 (14)	
Other, % (n)	0 (0)	5.0 (4)	
Concomitant intraabdominal injury and pelvic fracture			
Liver, % (n)	30.8 (4)	18.8 (15)	0.456
Spleen, % (n)	7.7 (1)	8.8 (7)	1
Pancreas, % (n)	7.7 (1)	1.3 (1)	0.261
Kidney, % (n)	0 (0)	11.3 (9)	0.351
Pelvic fracture, % (n)	7.7 (1)	21.3 (17)	0.451
Surgery, % (n)	100 (13)	28.7 (23)	<0.001
Angiographic embolization	0 (0)	33.8 (27)	0.017
Days in hospital	15 (12.5–39.8)	14.0 (7.0–42.0)	0.413
Mortality, % (n)	0 (0)	6.5 (6)	0.590

AIS = Abbreviated Injury Score, GCS = Glasgow Coma Scale, ISS = Injury Severity Score. Data are represented as median (interquartile range).

(AIS) ≥3 were 17 (interquartile range: 9.0–27.0) and 31%, respectively. These patients were involved in motor vehicle accidents (79.6%), had fallen (16.1%), or had other causes of injury (4.3%). Overall, the rate of exploratory surgery was 38.7% (n=36), and the mortality within 28 days was 6.5% (all deaths not related to HVI). None of the patients had undergone diagnostic peritoneal lavage. Of the patients who underwent exploratory surgery, 25% (n=9) received diagnostic laparoscopy. Among them, 4 patients (44%) converted to laparotomy to repair the HVI. Besides diagnostic laparoscopy, there were 4 (4.3%) unnecessary laparotomies and no delayed laparotomy in this study. The other 27 patients (29.0%) underwent angiographic embolization. Among these patients, 14 patients (51.9%) received angiographic embolization for hemostasis of pelvic fractures. Concomitant injuries included liver injury and pelvic fracture in approximately 20% of patients.

HVI was diagnosed in 13 patients (14%), and non-HVI was diagnosed in 80 patients (86.0%). In the HVI group, 7 patients (53.8%) had isolated HVI without concomitant intraabdominal injuries. The rate of operative exploration and AIS ≥3 was significantly higher in patients with HVI than that in patients with non-HVI (100% vs. 28.7%, $P < 0.001$; 100% vs. 24.2%, $P < 0.001$, respectively). The rate of angiographic embolization was significantly lower in patients with HVI than in patients with non-HVI (0% vs. 33.8%, $P < 0.017$). There were no significant differences between the other characteristics and in-hospital mortality between the 2 groups.

3.2. Vital signs, clinical presentations, and physical findings

The diagnostic findings are shown in Table 2. For vital signs, the respiratory rate was not used because it was difficult to measure and might be inaccurate. There was no significant difference in vital signs between the 2 groups. The most common presentation upon physical examination was tenderness (38.7%), followed by peritonitis sign (19.4%). The rate of both findings was significantly higher in patients with HVI than that in patients with non-HVI ($P < 0.05$). Peritonitis sign was strongly associated with HVI (odds ratio [OR] 17.75; 95% confidence interval [CI]: 4.53–69.63).

3.3. Laboratory findings

All biomarker levels except HGB were abnormal in both groups. Only the I-FABP level was significantly higher in patients with HVI than in those without HVI (9.92 [6.17–18.3] ng/mL vs. 3.97 [2.08–8.61] ng/mL, $P = 0.014$). However, all other biomarker levels did not significantly differ between groups. ROC analysis showed that the AUC was highest for I-FABP (AUC=0.71) in diagnosing HVI. Using the I-FABP best cutoff value (6.2 ng/mL), the sensitivity, specificity, positive predictive value, and negative predictive value were 76.9%, 70.0%, 29.4%, and 94.9%, respectively (OR 7.78; 95% CI: 1.97–30.79).

3.4. Radiological findings

The rate of positive FAST did not differ significantly between the 2 groups. Intravenous contrast media were used for all patients. The most common finding on CT was free fluid (51.6%). Of those with free fluid, only 18.8% had HVI. The presence of extraluminal air and bowel wall thickening was significantly higher in patients with HVI than in those without (OR 22.00; 95% CI: 4.50–107.59; OR 3.86; 95% CI: 1.07–13.98, respectively). The specificities were high

Table 2

Diagnostic findings with hollow viscus injury and non-hollow viscus injury.

	Hollow viscus injury (n=13)	Non-hollow viscus injury (n=80)	P
Vital sign			
Body temperature (°C)	36.1 (35.6–37.1)	36.1 (35.3–36.6)	0.334
Heart rate, beats/min	96.0 (110.0–80.0)	90.0 (76.8–108.3)	0.409
Systolic blood pressure, mmHg	117 (108.0–129.0)	121.0 (93.0–138.5)	0.670
Abdominal examination			
Tenderness, % (n)	79.9 (10)	32.5 (26)	0.004
Peritoneal sign, % (n)	69.2 (9)	11.2 (9)	<0.001
Biomarkers			
I-FABP, ng/mL	9.92 (6.17–18.3)	3.97 (2.08–8.61)	0.014
WBC (×10⁹ cells/L)	13.3 (11.0–15.6)	11.9 (8.2–16.1)	0.506
Hemoglobin, mg/dL	13.2 (11.7–14.2)	13.2 (11.7–17.5)	0.965
Lactate, mg/dL	46.0 (21.0–87.0)	29.5 (48.8–17.8)	0.195
AMY, U/L	87.0 (67.0–124.0)	78.0 (58.0–110.0)	0.386
Radiographic findings*			
FAST, % (n)	46.2 (6)	20.0 (16)	0.072
Extraluminal air, % (n)	46.2 (6)	3.8 (3)	<0.001
Free fluid, % (n)	69.2 (9)	48.8 (39)	0.235
Bowel wall thickening, % (n)	38.5 (5)	13.9 (11)	0.046
Contrast extravasation, % (n)	46.2 (6)	35.4 (28)	0.540
Solid organ injury, % (n)	30.8 (4)	28.7 (23)	1
No abnormalities, % (n)	0 (0)	27.5 (22)	0.034

AMY = amylase, FAST = focused Assessment with sonography for trauma, I-FABP = intestinal fatty acid binding protein, WBC = white blood cell count.
Median (interquartile range)
* All these findings are on computed tomography except for FAST.

(96.3%, 86.1%, respectively), but the sensitivities were low (46.2%, 38.5%, respectively). All patients with HVI had some kind of abnormal findings on CT, and the rate of no abnormal findings on CT was significantly lower in patients with HVI ($P = 0.034$). The lack of abnormal findings on CT had 100% sensitivity and a negative predictive value, but specificity was 27.5%. There were no significant differences in the other radiographic findings (free fluid, contrast extravasation, and solid organ injury) between the 2 groups.

3.5. Combination of I-FABP and other findings

The sensitivity, specificity, and positive and negative predictive value of I-FABP, peritonitis sign, and CT findings are shown in

Table 3

Sensitivity, specificity, and positive and negative predictive values of I-FABP, peritoneal sign, and CT findings in detecting hollow viscus injury.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
I-FABP	76.9	70.0	29.4	94.9
Peritoneal sign	69.2	88.8	50.0	94.7
Either I-FABP or peritoneal sign	100	61.3	29.5	100
Extraluminal air on CT	46.2	96.3	66.7	91.7
Bowel wall thickening on CT	38.5	86.1	31.3	89.5
No abnormality on CT	100	27.5	18.3	100
Both I-FABP and extraluminal air on CT	30.8	100	100	89.9

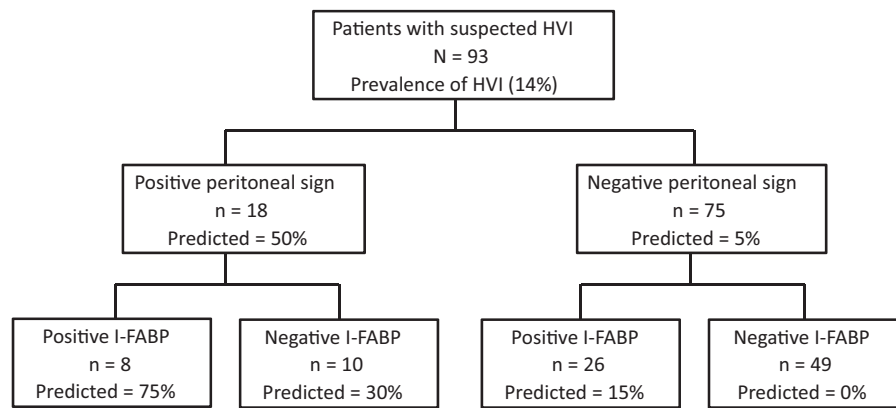CT = computed tomography, I-FABP = intestinal fatty acid binding protein.

Figure 1. Decision tree using I-FABP and physical examination for the management of patients with suspected HVI. HVI = hollow viscus injury, I-FABP = intestinal fatty acid–binding protein.

Table 3. Because the accuracy of I-FABP alone was insufficient, we hypothesized that the combination of I-FABP with other findings was better. To improve the sensitivity, I-FABP was combined with peritonitis sign. Figure 1 shows the relationship between I-FABP and peritonitis sign findings for predicting HVI. Among this study population, 52.7% of patients (n=49) had a negative I-FABP (<6.2 mg/dL) and a negative peritonitis sign, and none of them developed HVI (sensitivity, 100% and negative predictive value, 100%; $P < 0.001$). Similarly, to improve specificity, I-FABP was combined with extraluminal air findings on CT. Figure 2 shows the relationship between I-FABP and extraluminal air findings on CT for predicting HVI. In this study population, 4.3% (n=4) of patients had a positive I-FABP (>6.2 mg/dL) and extraluminal air on CT, and all of these patients developed HVI (specificity, 100% and positive predictive value, 100%; $P < 0.001$).

4. Discussion

This is the first study that demonstrates the diagnostic value of I-FABP and its value as a biomarker for HVI. HVI in blunt trauma patients is challenging to diagnose. The incidence of morbidity and mortality increases with time to operative intervention.[1] Currently, nonoperative management has become the treatment standard for mild solid organ injury that is hemodynamically stable, and it increases the risk of HVI, which always requires surgery. However, there is currently no reliable method to diagnose HVI in blunt trauma patients. A revised management strategy and new techniques are required to assist in diagnosing HVI. The largest study of 275,557 blunt trauma patients reported that current HVI diagnostic approaches lacked sensitivity.[2] However, the present study demonstrated that a combination of peritonitis and I-FABP had 100% sensitivity for diagnosing HVI. This means that for patients with negative I-FABP and negative peritonitis signs, HVI can be ruled out at the time of admission. Patients without other injuries can be discharged immediately.

Although there are many studies on the diagnosis of HVI, most are retrospective studies, and there are few studies to date that combine CT findings, laboratory findings, and physical findings to diagnose HVI. It is difficult to study prospectively because blunt HVI is relatively rare and the incidence is <1%.[19] In the present study, HVI occurred in only 0.6% of patients with abdominal CT. The low incidence and lack of experience make it difficult to diagnose HVI. Some studies reported that solid organ injuries, seat belt sign, and injury mechanisms related to the abdomen are associated with an increased risk of HVI.[2,20,21] Thus, the probability of diagnosing HVI in this study increased by 14.0% in this patient population. Surgeons should perform a thorough examination of blunt trauma patients who have these findings that may suggest HVI.

For blunt trauma patients, the presence of plasma biomarkers has long served as a diagnostic tool for organ injuries, especially
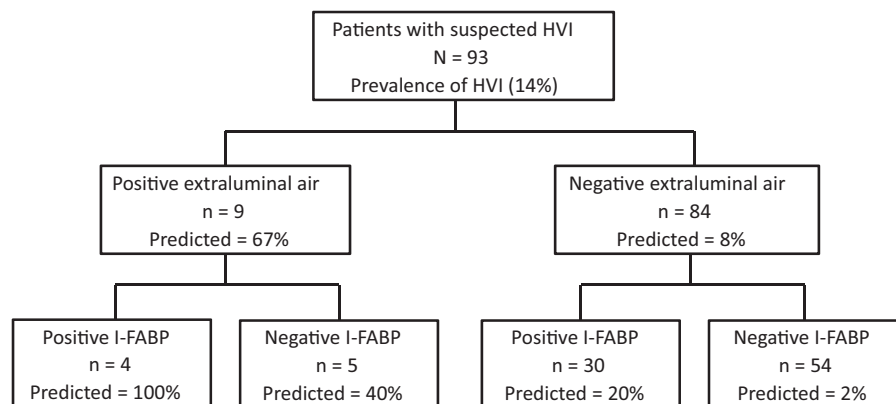

Figure 2. Decision tree using I-FABP and extraluminal air on computed tomography for the management of patients with suspected HVI. HVI = hollow viscus injury, I-FABP = intestinal fatty acid–binding protein.

of the heart and liver.[22,23] Alanine aminotransferase and troponin I are used extensively, since quickly measuring these biomarkers in the plasma of emergency department patients can prove extremely useful for detecting heart and liver injuries. Additionally, heart-type FABP is widely used to treat acute myocardial infarction. Using the same mechanism as heart and liver injury, I-FABP, which is found exclusively in the intestinal mucosa, could possibly be released into the bloodstream following tissue injury.[24] Therefore, we aimed to improve the diagnosis of HVI using I-FABP. I-FABP is the only biomarker that is bowel membrane–specific, and it was also the top diagnostic performer in this study.

The diagnostic accuracy of I-FABP alone was insufficient for patients with HVI. I-FABP can be elevated in other types of bowel disease, such as small bowel obstruction, mesenteric ischemia, acute enterocolitis, Crohn disease, ulcerative colitis, and necrotizing enterocolitis.[7,11,12,25–27] Besides these factors, I-FABP can increase the false-positive rate in trauma patients. First, hemorrhagic shock and systemic inflammatory response are known to cause intestinal mucosal damage.[28] I-FABP levels increase in severe trauma patients without HVI.[13–16] Haan et al reported that the level of I-FABP was significantly related to the interleukin 6 level and the presence of shock. Second, I-FABP can be elevated in severe abdominal trauma to the diaphragm, liver, and spleen, without HVI.[13,15,16] I-FABP levels are significantly higher in patients with abdominal AIS ≥3 than in those with abdominal AIS <3. This might indicate that a direct blow to the abdomen affects I-FABP levels. I-FABP might also be released from a less severely injured bowel that does not require surgery, such as submucosal hematoma, bowel bruise, or a small serosal tear. In this present study, true bowel findings in patients with nonsurgical management were unavailable. These patients may have had a self-limited, unidentified bowel injury during their disease course. Therefore, surgeons should consider these false-positives when using I-FABP. We believe that I-FABP can play a more decisive role in hemodynamically stable blunt trauma patients.

Currently, CT is the most commonly used modality for diagnosing abdominal trauma, and it is regarded as highly accurate in identifying solid-organ injuries. However, the usefulness of CT for diagnosing HVI in blunt trauma patients remains controversial. With the development of the multidetector CT, HVI diagnosis may be more accurate. In a recent study that used multidetector CT for surgically important bowel and mesenteric injury after blunt trauma, sensitivities and specificities ranged from 87% to 95%, and 48% to 84%, respectively.[29] In the Eastern Association for the Surgery of Trauma (EAST) study of 3258 trauma patients with CT, 13% of blunt trauma patients with perforated small bowel injury had no abdominal findings.[2] In the present study, a high multidetector CT was used, and the accuracy was relatively high compared to previous studies. Extraluminal air on CT had a low sensitivity and a high specificity (46.2% and 96.3%, respectively). Although extraluminal air is classically a finding associated with HVI that requires surgery, recent studies reported that extraluminal air has a high false-positive rate (29%–61%) in blunt trauma patients.[2,29–31] Marek et al[30] demonstrated that free fluid, seat belt sign, or radiographic findings that suggest HVI in the presence of extraluminal air are highly predictive of HVI. The present study demonstrated that I-FABP has a high predictive value for diagnosing HVI in blunt trauma patients with extraluminal air on CT. Combined I-FABP and CT findings might be useful in diagnosing HVI.

CT is a useful modality for trauma management, but a plasma biomarker for trauma patients has various advantages compared to CT. First, CT is expensive and not uniformly available worldwide. Second, there are absolute or relative contra-indications in unstable patients or in performing intravenous contrast-enhanced CT, such as iodine contrast media allergy or renal failure. Third, interpretation of the results requires significant expertise and the inter-reader agreement is not high.[32] There are many suspicious findings on CT that may complicate the diagnosis. I-FABP is a simple and objective test and might be able to offset weaknesses in CT.

Using the I-FABP test alone or examination alone is insufficient for diagnosing HVI. Surgeons should make a comprehensive assessment that combines physical examination, laboratory, and radiographic findings to diagnose bowel injuries. McNutt et al[33] demonstrated that diagnostic accuracy for bowel injury becomes efficient via scoring using the Bowel Injury Prediction Score (BIPS). The BIPS includes physical examination, presence of leukocytosis, and CT findings. The sensitivity, specificity, negative predictive value, and positive predictive value were 85.7%, 76.2%, 70.6%, and 88.9%, respectively. Similarly, this present study showed that CT findings and physical examinations are useful for diagnosing HVI, but WBC was inconsistent. WBC is known to be unreliable, as previously reported.[2,6] Using I-FABP instead of WBC, the BIPS might be able to diagnose HVI more accurately.

The present study has several limitations. First, even though the study was conducted over 5 years, the number of patients with HVI was small. This could have magnified the effect of selection bias. It is difficult to increase the sample size because blunt HVI is rare.[19] Additionally, we could not analyze a diagnostic scoring system and perform a multivariate analysis because of concerns about the sample size. Multi-institutional studies will be useful in resolving this limitation. Second, physical examinations are more subjective compared to other tests. Many studies reported that physical examination is one of the most important factors for decision-making in emergency abdominal surgery. However, some studies reported that physical examinations have poor interobserver agreement (K value=0.4–0.7).[34–36] Therefore, several surgeons at our hospital carefully performed a physical examination. Third, this study did not take into account the time and amount of bowel injuries. Biomarker levels may correlate with the amount of bowel injuries and time. Currently, many biomarkers are available at trauma centers, and each biomarker has its distinctive character-istics (e.g., WBC increases when collecting serial samples after admission).[6] However, I-FABP might have a peak at admission.[13–15] Serial I-FABP test is required to diagnose HVI.

5. Conclusions

This is the first study to demonstrate the diagnostic value of a biomarker for HVI. I-FABP has a higher negative predictive value compared to traditional diagnostic tests. However, the accuracy of I-FABP alone was insufficient to diagnose HVI in abdominal blunt trauma patients. Surgeons should make a comprehensive assessment. The combination of I-FABP and physical examina-tion may be able to rule out HVI without requiring a CT scan.

References

[1] Fakhry SM, Brownstein M, Watts DD, et al. Relatively short diagnostic delays (<8 hours) produce morbidity and mortality in blunt small bowel injury: an analysis of time to operative intervention in 198 patients from a multicenter experience. J Trauma 2000;48:408–14.

[2] Fakhry SM, Watts DD, Luchette FA. Current diagnostic approaches lack sensitivity in the diagnosis of perforated blunt small bowel injury: analysis from 275,557 trauma admissions from the EAST multi-institutional HVI trial. J Trauma 2003;54:295–306.

[3] Crookes BA, Shackford SR, Gratton J, et al. "Never be wrong": the morbidity of negative and delayed laparotomies after blunt trauma. J Trauma 2010;69:1386–91.

[4] Renz BM, Feliciano DV. Unnecessary laparotomies for trauma: a prospective study of morbidity. J Trauma 1995;38:350–6.

[5] Morrison JE, Wisner DH, Bodai BI. Complications after negative laparotomy for trauma: long-term follow-up in a health maintenance organization. J Trauma 1996;41:509–13.

[6] Schnuriger B, Inaba K, Barmparas G, et al. Serial white blood cell counts in trauma: do they predict a hollow viscus injury? J Trauma 2010;69:302–7.

[7] Cronk DR, Houseworth TP, Cuadrado DG, et al. Intestinal fatty acid binding protein (I-FABP) for the detection of strangulated mechanical small bowel obstruction. Curr Surg 2006;63:322–5.

[8] Thuijls G, van Wijck K, Grootjans J, et al. Early diagnosis of intestinal ischemia using urinary and plasma fatty acid binding proteins. Ann Surg 2011;253:303–8.

[9] Kanda T, Tsukahara A, Ueki K, et al. Diagnosis of ischemic small bowel disease by measurement of serum intestinal fatty acid-binding protein in patients with acute abdomen: a multicenter, observer-blinded validation study. J Gastroenterol 2011;46:492–500.

[10] Matsumoto S, Sekine K, Funaoka H, et al. Diagnostic performance of plasma biomarkers in patients with acute intestinal ischaemia. Br J Surg 2014;101:232–8.

[11] Lieberman JM, Sacchettini J, Marks C, et al. Human intestinal fatty acid binding protein: report of an assay with studies in normal volunteers and intestinal ischemia. Surgery 1997;121:335–42.

[12] Kanda T, Fujii H, Tani T, et al. Intestinal fatty acid-binding protein is a useful diagnostic marker for mesenteric infarction in humans. Gastroenterology 1996;110:339–43.

[13] Relja B, Szermutzky M, Henrich D, et al. Intestinal-FABP and liver-FABP: novel markers for severe abdominal injury. Acad Emerg Med 2010;17:729–35.

[14] de Haan JJ, Lubbers T, Derikx JP, et al. Rapid development of intestinal cell damage following severe trauma: a prospective observational cohort study. Crit Care 2009;13:R86.

[15] Timmermans K, Sir O, Kox M, et al. Circulating iFABP Levels as a marker of intestinal damage in trauma patients. Shock 2015;43:117–20.

[16] Voth M, Holzberger S, Auner B, et al. I-FABP and L-FABP are early markers for abdominal injury with limited prognostic value for secondary organ failures in the post-traumatic course. Clin Chem Lab Med 2015;53:771–80.

[17] ATLS Subcommittee; American College of Surgeons' Committee on Trauma; International ATLS working groupAdvanced trauma life support (ATLS (R)): the ninth edition. J Trauma Acute Care Surg 2013;74:1363–6.

[18] Funaoka H, Kanda T, Kajiura S, et al. Development of a high-specificity sandwich ELISA system for the quantification of human intestinal fatty acid-binding protein (I-FABP) concentrations. Immunol Invest 2011;40:223–42.

[19] Watts DD, Fakhry SM. Incidence of hollow viscus injury in blunt trauma: an analysis from 275,557 trauma admissions from the East multi-institutional trial. J Trauma 2003;54:289–94.

[20] Bronner JF, Boissel P. [Acute ischemia and arterial mesenteric infarction in patients aged over 75. Apropos of a comparative series of 38 cases]. J Chir (Paris) 1997;134:109–13.

[21] Chandler CF, Lane JS, Waxman KS. Seatbelt sign following blunt trauma is associated with increased incidence of abdominal injury. Am Surg 1997;63:885–8.

[22] Velmahos GC, Karaiskakis M, Salim A, et al. Normal electrocardiography and serum troponin I levels preclude the presence of clinically significant blunt cardiac injury. J Trauma 2003;54:45–50.

[23] Srivastava AR, Kumar S, Agarwal GG, et al. Blunt abdominal injury: serum ALT-A marker of liver injury and a guide to assessment of its severity. Injury 2007;38:1069–74.

[24] Pelsers MM, Hermens WT, Glatz JF. Fatty acid-binding proteins as plasma markers of tissue injury. Clin Chim Acta 2005;352:15–35.

[25] Sarikaya M, Ergul B, Dogan Z, et al. Intestinal fatty acid binding protein (I-FABP) as a promising test for Crohn's disease: a preliminary study. Clin Lab 2015;61:87–91.

[26] Wiercinska-Drapalo A, Jaroszewicz J, Siwak E, et al. Intestinal fatty acid binding protein (I-FABP) as a possible biomarker of ileitis in patients with ulcerative colitis. Regul Pept 2008;147:25–8.

[27] Heida FH, Hulscher JB, Schurink M, et al. Intestinal fatty acid-binding protein levels in Necrotizing Enterocolitis correlate with extent of necrotic bowel: results from a multicenter study. J Pediatr Surg 2015;50:1115–8.

[28] Moore FA. The role of the gastrointestinal tract in postinjury multiple organ failure. Am J Surg 1999;178:449–53.

[29] Akyildiz H, Akcan A, Ozturk A, et al. D-dimer as a predictor of the need for laparotomy in patients with unclear non-traumatic acute abdomen. A preliminary study. Scand J Clin Lab Invest 2008;68:612–7.

[30] Marek AP, Deisler RF, Sutherland JB, et al. CT scan-detected pneumoperitoneum: an unreliable predictor of intra-abdominal injury in blunt trauma. Injury 2014;45:116–21.

[31] Kobold S, Luetkens T, Cao Y, et al. Prognostic and diagnostic value of spontaneous tumor-related antibodies. Clin Dev Immunol 2010;2010:721531.

[32] Butela ST, Federle MP, Chang PJ, et al. Performance of CT in detection of bowel injury. AJR Am J Roentgenol 2001;176:129–35.

[33] McNutt MK, Chinapuvvula NR, Beckmann NM, et al. Early surgical intervention for blunt bowel injury: the Bowel Injury Prediction Score (BIPS). J Trauma Acute Care Surg 2015;78:105–11.

[34] Kalfa N, Zamfir C, Lopez M, et al. Conditions required for laparoscopic repair of subacute volvulus of the midgut in neonates with intestinal malrotation: 5 cases. Surg Endosc 2004;18:1815–7.

[35] Fong KY, Siao FY, Yen HH. Cecal pneumatosis intestinalis in obstructing sigmoid cancer: emergency metallic stenting. Am J Emerg Med 2014;32:391–3. 395 e.

[36] Pines J, Uscher Pines L, Hall A, et al. The interrater variation of ED abdominal examination findings in patients with acute abdominal pain. Am J Emerg Med 2005;23:483–7.