Blunt Abdomen Trauma and Biomarkers

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Contents

Abstract

Blunt abdomen trauma (BAT) consists of one of the major emergencies that can result in a wide range of severity from mild simple stable to potentially life-threatening conditions. Recognition of the injury of the particular organ and the grading of the injury as early as possible is one of the keys to management of the blunt abdomen trauma. The recognition of biomarkers in diagnosis and management of BAT is trending slowly. The use of biomarkers in blunt abdomen trauma is still in its early stage, and no standard practice has been established till date. Several biomarkers are reported for specific organ injury in BAT and also several biomarkers are reported for overall prediction of the prognosis of the patients with severe BAT. In this chapter, we discuss the developments in various biomarkers for BAT and its fundamental application that can help the modern physician to provide supplementary arsenal in diagnosis and management of BAT.

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Keywords

Abdomen · Application · Biomarker · Blunt · Hollow · Kidney · Liver · Pancreas · Prognosis · Trauma · Viscus

Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
ATLS	Advanced Trauma Life Support
BAT	Blunt abdomen trauma
CRP	C-reactive protein
CT	Computed tomography
Cys-C	Cystatin-C
HMGB-1	High mobility group box-1
HVI	Hollow viscus injury
I-FABP	Intestinal fatty acid-binding protein
IL-18	Interleukin 18
KIM-1	Kidney injury molecule-1
LDH	Lactate dehydrogenase
NGAL	Neutrophil gelatinase-associated lipocalin
NLRP3	NACHT domain-, leucine-rich repeat-, and PYD-containing protein 3
PCT	Procalcitonin
WHO	World Health Organization

Introduction

Blunt abdomen trauma (BAT) consists of one of the major emergencies that require urgent care and specialized consultation. They can result in a wide range of severity from mild simple stable to potentially life-threatening conditions. It presents a major challenge to the attending emergency physicians and surgeons (Smyth et al. 2022). The basic mechanism of blunt abdomen trauma can have a spectrum of effect from particular organ to multiple organ injury including musculoskeletal system. Recognition of the injury of the particular organ and the grading of the injury as early as possible is one of the keys to management of the blunt abdomen trauma. With the development of ATLS (Advanced Trauma Life Support), the advancement in the management of trauma has taken a giant leap. With the introduction of several protocols and imaging investigations, the management of blunt abdomen trauma has improved within short duration. The recognition of biomarkers in diagnosis and management of BAT is trending slowly.

The World Health Organization (WHO), in coordination with the United Nations and the International Labor Organization, has defined a biomarker as "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" (Nations et al. 2014). The use biomarkers in blunt abdomen trauma are still in its early stage and no standard practice has been

Table 1 List of all the possible organ specific biomarkers for diagnosis in BAT

Organs	Biomarkers
Liver	ALT, AST, LDH
Kidney	NGAL, KIM-1, Renalase, IL-18, Cys-C
Hollow viscus organs	I-FABP, NLRP3, HMGB-1
Pancreas	Amylase, lipase

ALT alanine transaminase, *AST* aspartate transaminase, *CRP* C-reactive protein, *Cys-C* cystatin-C, *HMGB-1* high mobility group box-1, *IL-18* interleukin 18, *I-FABP* intestinal fatty acid-binding protein, *KIM-1* kidney injury molecule-1, *LDH* lactate dehydrogenase, *NGAL* neutrophil gelatinase-associated lipocalin, *NLRP3* NACHT domain, leucine-rich repeat-, and PYD-containing protein 3, *PCT* procalcitonin

established till date. In this chapter we will discuss about application of biomarkers in BAT (Table 1).

Biomarkers for Liver Injury

Aspartate Transaminase (AST) and Alanine Transaminase (ALT) Transaminases are mitochondrial and cytoplasmic enzymes. AST and ALT are present in hepatocytes in high concentration, and following BAT, they leak into blood circulation. Their main function is to catabolize amino acids, permitting them to enter the citric acid cycle. AST is typically found in the liver only but ALT is also found in the heart skeletal muscle, kidney, brain, and RBC. Recently AST and ALT both have been studied extensively for its application to diagnose liver injury in BAT. Where computed tomography (CT) scan is available, it is considered the gold standard for the diagnosis of liver injury in BAT (Fig. 1) (Iacobellis et al. 2019). In the remote and periphery centers where CT scan is not available, AST and ALT may provide valuable guidance to the emergency physician to suspect liver trauma. Patients will be greatly benefitted from on timely referral of the patient to the tertiary trauma center (Shrestha et al. 2021).

Application to BAT: Koyoma et al. reported the optimal cut-off values of AST and ALT were 109 U/l and 97 U/l, respectively, for the patients with liver injury in blunt abdominal trauma. They suggested the optimal cut-off value as a predictor and also screening tool for CT scans for the presence of liver injury (Koyama et al. 2016). Recently various studies have shown that AST and ALT are some of the valuable biomarkers for liver injury in blunt abdominal trauma (Shrestha et al. 2021; Chang et al. 2017). These studies not only report that AST and ALT are important biomarkers for diagnosis of liver injury in BAT, they also suggested that the level of AST and ALT also helps to predict the severity of the liver injury. The higher the level of AST and ALT, the grade of liver injury increased accordingly (Shrestha et al. 2021). The cut-off value of various researches has been given in Table 2.

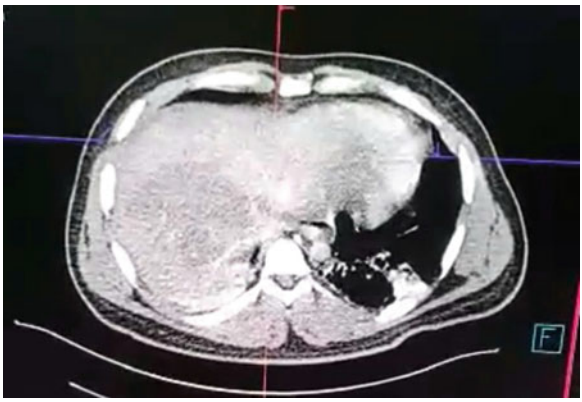

Fig. 1 CT scan showing injury of the right lobe of liver due to BAT (Courtesy of Dr. Yuvraj Raut, Chitwan Medical College Teaching Hospital, Department of Radiology, Chitwan, Nepal)

Table 2 List of cut-off value of AST and ALT by different authors for liver injury in BAT

Authors with publication year	Cut-off level for AST (U/L)	Cut-off level for ALT (U/L)
Tan et al. (2009)	82	126
Lee et al. (2010)	60	58
Tian et al. (2012)	113	57
Koyama et al. (2016)	109	97
Chang et al. (2017)	200	125
Shrestha et al. (2021)	106	80

ALT alanine transaminase, *AST* aspartate transaminase

Lactate Dehydrogenase (LDH) LDH is a cytoplasmic enzyme that is expressed in almost all major organ systems. It is released into the peripheral blood following cell death caused by ischemia or injury, for example. Because of its ubiquitous expression, the total serum LDH level is a highly sensitive, but nonspecific test.

Application to BAT: In the study done by Bilgic et al. the LDH level on admission was correlated with mortality and the severity of liver injury. It was also independently associated with mortality in multivariate analysis. High LDH levels may reflect the number of affected organs and the severity of injury (Bilgic et al. 2014). Similarly the study done by Tan et al. reported that patients with normal ALT, AST, and LDH are unlikely to have major liver injuries (Tan et al. 2009). It is advised that LDH can be used together with AST and ALT as a complementary test for liver injury in patients with blunt abdominal trauma. It cannot be used as diagnostic test since CT scan is the gold standard for the diagnosis of liver injury in blunt abdominal trauma (Iacobellis et al. 2019).

Biomarkers for Kidney Injury

Renal injuries are suspected frequently among patients who sustain blunt abdominal trauma. About 8 to 10 percent of the total patients presenting with blunt abdominal trauma was diagnosed with kidney injury (Alonso et al. 2009; Harris et al. 2001). Children are especially prone to blunt renal injuries because of the small proportion of retroperitoneal and abdominal fat tissue (Brown et al. 1998). The kidney size, the weak expression of muscles, the elastic ribs, and their anatomical position are the factors which add additional risk for blunt renal injury (Hirsch et al. 2017). Ultrasonography is the diagnostic method of choice for the examination of traumatic renal injury for children, and in case of severe injury, CT scan could be considered (Amerstorfer et al. 2015). For adults, CT is the technique of choice for evaluating the renal trauma as it can give accurate information about the status of the renal parenchyma, blood vessels, and collecting system (Bonatti et al. 2015; Park et al. 2012). Recently some of the new biomarkers have been reported for kidney injury in BAT.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) NGAL is a 25 kDa protein belonging to the lipocalin family (Singer et al. 2013). The role of NGAL has been well established in patients with burn as a biomarker for acute kidney injury (Hong et al. 2013; Sen et al. 2015).

Application to BAT: Even though study in human population has not been done, promising reports on rat models have been done. In the experimental rat model study conducted by Bakal et al. they found that both serum and urinary level of NGAL were significantly increased immediately after the trauma. They concluded that the NGAL was an important noninvasive biomarker in the early recognition of blunt renal trauma (Bakal et al. 2019).

Kidney Injury Molecule-1 (KIM-1) KIM-1 is a type 1 trans-membrane protein, with an immunoglobulin and mucin domain, whose expression is markedly upregulated in the proximal tubule in the post-ischemic rat kidney. It was first reported by Ichimura et al. that KIM-1 was not present at a detectable level in normal rat kidneys, whereas it was increased in the kidneys of rats after acute renal ischemia (Ichimura et al. 1998). Similarly, another study indicated that urinary KIM-I might be preferable to conventional biomarkers in human studies as a noninvasive, rapid, sensitive, reproducible, and potentially high-throughput method to detect early kidney injury (Vaidya et al. 2006).

Application to BAT: No human studies have been done for the diagnostic utility of KIM-1 as biomarker for detecting blunt renal trauma. In the same experimental study conducted by Bakel et al. in rat model for NGAL, they reported there was a significant difference in the KIM-1 values after blunt renal trauma (Bakal et al. 2019). KIM-1 has shown positive evidence for the future research as a biomarker for blunt renal trauma.

Interleukin 18 (IL-18) Interleukin-18 (IL-18) was first described as "IFNg-inducing factor" in 1989 as a pro-inflammatory cytokine that is structurally and functionally related to the IL-1 family (Dinarello et al. 2013). A role for IL-18 has been implicated in several diseases, including renal injury (Leslie and Meldrum 2008).

Application to BAT: IL-18 is also one of the promising potential noninvasive biomarkers for blunt renal trauma. Like NGAL and KIM-1, this biomarker has not been studied in human population. In the study conducted by Bakel et al. in rat model, they reported that urine IL-18 levels of the blunt renal trauma group were significantly higher than those of the sham and control groups. However, serum IL-18 levels were significantly higher in both the sham and trauma groups compared with the control group (Bakal et al. 2019). Therefore, elevated serum levels of IL-18 do not seem to be associated with blunt renal trauma, and detailed clinical and experimental studies are needed to determine the potential utility of these markers in routine care.

Cystatin-C (Cys-C) Cystatin C (CysC) is a 13-kDa endogenous cysteine proteinase inhibitor produced at a constant rate by all nucleated cells and eliminated by glomerular filtration (Herget-Rosenthal et al. 2000). Hence, serum CysC is an early biomarker of AKI that can reflect the early changes in renal function and the decline of GFR (Liu et al. 2016). In traumatic hemorrhagic shock, CysC is significantly increased in the early stage of the shock and CysC can be used as a marker to predict AKI (Chen et al. 2015).

Application to BAT: Recently CysC has also been studied as a possible biomarker for blunt renal trauma. In the study done by Bakel et al. in the trauma group, serum and urine Cys-C levels reached their highest level within 60–72 h. They reported that although Cys-C levels do not seem to be beneficial in the early detection of trauma, they could be useful during the monitoring of the patient (Bakal et al. 2019). The limitation of this biomarker needs to be further studied in order to be used as a biomarker for kidney injury in BAT.

Renalase In 2005, the identification of renalase was reported. The human kidney releases this protein into the bloodstream to regulate blood pressure and breaks down catecholamines like adrenaline and noradrenaline in the blood circulation (Xu et al. 2005).

Application to BAT: Its role as a supplement in diagnosing of renal injury in blunt abdomen trauma is still in preliminary phase. Recently, the levels of renalase for the diagnosis of renal injury in rats with experimentally induced blunt renal trauma were investigated (Saraç et al. 2021). They reported that the level of renalase increased significantly in the rats grouped with blunt renal trauma (Saraç et al. 2021). Further studies are needed to be done for this biomarker.

Biomarkers for Pancreatic Injury Due to its retroperitoneal position, the injury to the pancreas in BTA is often difficult to diagnose. CT scan is the gold standard for diagnosing pancreatic injury in BTA. Serum amylase and serum lipase have been used as a diagnostic tool to diagnose acute pancreatitis. The use of serum lipase and amylase in the diagnosis of blunt pancreatic injury can be quiet challenging as the level of these enzymes may significantly increase in several other non-pancreatic-related conditions.

Serum Amylase and Lipase Amylase, a digestive enzyme, is predominantly secreted by the pancreas and salivary glands. Amylases' main function is to hydrolyze the glycosidic bonds in starch molecules, converting complex carbohydrates to simple sugars (Peyrot des Gachons and Breslin 2016). Serum amylase is elevated in a variety of conditions, including pancreatic disease, salivary disease, decreased metabolic clearance, intestinal disease, and macroamylasemia. It is one of the important criteria for diagnosing acute pancreatitis (Banks et al. n.d.). Lipase is an enzyme that is present in pancreatic secretions which breaks down triglycerides into free fatty acids and glycerol. They play a vital role in fat digestion. The increase in serum lipase can be seen in various pathologies like acute pancreatitis, chronic pancreatitis, peritonitis, small intestine manipulation, etc.

Application to BAT: Recently various studies have been reported as their role in blunt pancreatic injury. In the recent study reported from the Republic of Iran, they reported comparison of laboratory findings of amylase enzymes in patients with internal organ and pancreatic damage were higher than in patients without internal organ injury (Hosseininejad et al. 2020). Out of 384 patients, the patients diagnosed with pancreatic injury by focused assessment with sonography for trauma (FAST) scan, CT scan, and laparotomy had mean serum amylase level of 157.96, 83.47, and 93.42, respectively. There was statistical difference in mean amylase level between the non-pancreatic injury and pancreatic injury group. Similarly, serum lipase level was also higher in patients with blunt pancreatic trauma. The mean serum lipase level was 118.89 in patients with pancreatic injury. This suggests that measuring these enzymes could support the clinical suspicion of pancreatic damage as a reliable and cost-effective screening method in countries with limited resources where CT scan is not available. This may help the surgeons and emergency physicians to take proper measures in management of these patients. Similarly, a study done in India has also reported similar findings with some extra guidelines. Mahajan et al. have reported that combined serum amylase and lipase showed 100% specificity and 85% sensitivity in predicting pancreatic injury (Mahajan et al. 2014). The mean values of serum amylase in patients with low-grade injuries were 733 compared to 1323 in the high-grade group. For serum lipase, the corresponding figures were 618 and 1051, respectively. Elevated vs. normal serum amylase and lipase levels showed sole statistically significant association with time elapse since injury to admission, with a cut-off of 3 hours. They also pointed the time frame that persistently elevated or rising combined estimation of serum amylase and lipase levels are reliable indicators of pancreatic injury and is time dependent, non-diagnostic within 6 h or less after trauma.

Biomarker for Hollow Viscus Injury (HVI) CT has been shown to be accurate for the diagnosis of bowel and mesenteric injuries and is the diagnostic test of choice in the evaluation of BAT in hemodynamically stable patients. Sometimes injury to the hollow viscus is only found during laparotomy (Fig. 2).

Intestinal Fatty Acid-Binding Protein (I-FABP) The biomarkers for the HVI are the least explored one. The increase in WBC count has been studied as a biomarker for HVI in the first 24 hours. But the delay in diagnosis of HVI even for more than 8 hours has a very poor prognosis. Usually CT scan are considered gold standard for HVI. Recently I-FABP have been the point of interest by many researchers as a biomarker for intestinal diseases. 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 (Gajda and Storch 2015). I-FABP is elevated in several types of bowel disease, such as small bowel obstruction, mesenteric ischemia, acute enterocolitis, Crohn's disease, ulcerative colitis, and necrotizing enterocolitis (Cronk et al. 2006; Heida et al. 2015; Lieberman et al. 1997; Sarikaya et al. 2015; Wiercinska-Drapalo et al. 2008).

Application to BAT: Till now only one study has reported I-FABP as a potential biomarker for HVI in BAT (Matsumoto et al. 2017). The mean I-FABP was 9.92 ng/ml in patients with HVI and in patients with non-HVI was 3.97 ng/ml. The sensitivity of I-FABP was 76.9% and specificity 70.0%. Because the accuracy of I-FABP alone was insufficient, they combined the I-FABP with peritonitis sign to improve the sensitivity. None of the patients with negative I-FABP and a negative peritonitis sign developed HVI for which sensitivity was 100% and negative predictive value was 100%. Similarly, to improve specificity, I-FABP was combined with extra-luminal air findings on CT. The patients had both a positive I-FABP and extra-luminal air on CT, all of those patients developed HVI with specificity of 100%

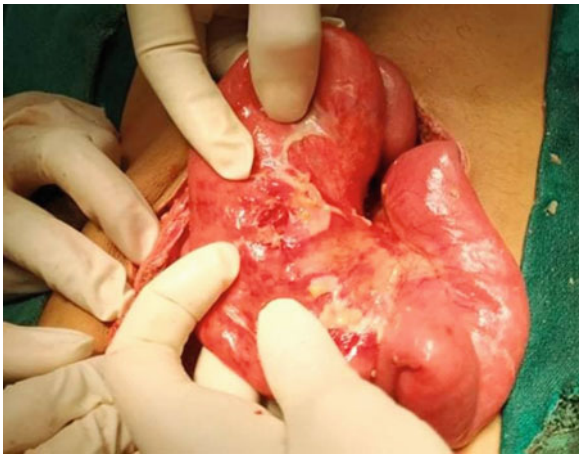

Fig. 2 Jejunal perforation due to BAT (courtesy of Dr. Dilip Baral, Department of Surgery, Pokhara Military Hospital, Pokhara, Nepal)

and positive predictive value of 100%. They suggested that for patients with negative I-FABP and negative peritonitis signs, HVI can be ruled out at the time of admission and patients with both a positive I-FABP and extra-luminal air on CT, diagnosis of HVI should be strongly considered. We conclude that the combination of I-FABP and physical examination may be able to rule out HVI. Further studies should be done in high-volume centers.

Biomarkers for Prognosis of the Patients with Severe BAT The diagnosis of blunt abdomen trauma is not only important; the proper protocol for the management of BAT is very crucial. During management of the BAT, determining prognosis of the patients with BAT is also very important.

NLRP3 and High Mobility Group Box-1 (HMGB-1) HMGB-1, a member of the alarmin group of cellular messaging proteins, is a pro-inflammatory cytokine that has been proven to be associated with post-traumatic inflammation (Yang et al. 2015). Studies have demonstrated that NACHT domain-, leucine-rich repeat-, and PYD-containing protein 3 (NLRP3) plays an important role in HMGB-1-mediated inflammation in many diseases and bioprocesses. NLRP3 can facilitate in vivo HMGB-1 release, and HMGB-1 can induce an increase in the level of IL-1b by activating the NLRP3 inflammasome.

Application to prognosis of BAT: In the study done by Sun and Xia et al. they demonstrated that the serum levels of NLRP3 and HMGB-1 were significantly higher in all BAT patients than in the healthy controls, and the serum levels of NLRP3 and HMGB-1 were significantly higher in the severe BAT group than in the mild/moderate BAT group (Sun and Xia 2019). They also reported that serum levels of NLRP3 and HMGB-1 were significantly higher in the deceased patients than in the living patients, suggesting that NLRP3 and HMGB-1 levels might be associated with death in severe BAT patients. They also reported that serum levels of NLRP3 and HMGB-1 were correlated with 6-month mortality in severe BAT patients. We strongly suggest that NLRP3 and HMGB-1 can play a significant role in determining the prognosis of the patients with severe BAT and multi-institutional study is required for its validity.

C-Reactive Protein (CRP) CRP is an acute-phase reactant protein synthesized by the liver, whose level rises in response to inflammation (Du Clos 2000). It is primarily induced by the IL-6 action on the gene responsible for the transcription of CRP during the acute phase of an inflammatory/infectious process (Sproston and Ashworth 2018). The alteration of baseline CRP levels are affected by many factors including age, gender, smoking status, weight, lipid levels, and blood pressure (Hage and Szalai 2007). The average levels of serum CRP in a healthy adult is around 0.8 mg/L. There is growing evidence of usefulness of CRP to predict prognosis in septic shock patients in ICU. The patients with dropping CRP level after admission had better prognosis than the patients whose CRP level didn't drop. The cut-off value of CRP for diagnostic accuracy of severe sepsis in critical patients was found to be 61 mg/L (Anush et al. 2019; Pradhan et al. 2016).

Application to prognosis of BAT: The role of CRP in prognosis of patients with trauma has been studied especially in pediatric population (Brunengraber et al. 2009). They reported that monitoring of the early CRP would correlate with clinical morbidity and outcome measures in pediatric trauma patients and also in estimating injury severity early in hospitalization. One study stated a controversial report that CRP is not valuable in adult population with BAT (Giannoudis et al. 2009). Still reliable study is needed to done for CRP to mark as a biomarker for predicting prognosis of patient with BAT.

Procalcitonin (PCT) Serum PCT a protein is the peptide precursor of calcitonin, a hormone that is synthesized by the parafollicular C cells of the thyroid and involved in calcium homeostasis. Although PCT is usually produced in the thyroid, during bacterial infections it is released by the neuro-endocrine cells of the lung and intestine and as an acute-phase reactant (Davies 2015). Studies have shown that, in ICU patients with sepsis, higher PCT levels are associated with a greater risk of progression to severe sepsis and septic shock, worsening the survival prognosis (Gregoriano et al. 2020; Rajkumari et al. 2013; Vijayan et al. 2017).

Application to prognosis of BAT: Recently PCT has recently become of interest as a possible marker for the prognosis of patients with severe trauma including abdomen trauma (Castelli et al. 2009; Maier et al. 2009; Sakran et al. 2012; Wanner et al. 2000). PCT has also been used as an independent prognostic biomarkers in children with severe trauma (Weber et al. 2021). Initial elevation of PCT is transient and after 48 hours they tend to decrease. During this time frame, higher serum PCT levels appear to indicate a poorer prognosis in patients (Koutroulis et al. 2014). In the recent review done by Alrawahi et al. they suggested that early rise of serum PCT may be used as an early predictor of severe injury, development of sepsis and MOD, and mortality in trauma population. They also indicated that patients with high level of PCT are warranted for aggressive management to prevent high morbidity and mortality (Alrawahi et al. 2019). However all these studies are not specific to blunt abdomen trauma. Multicenter prospective trials are needed to investigate the impact of PCT-guided decision-making on the clinical outcomes in the BAT setting.

Unsolved Mysteries

We all know that splenic injury is the most common organ injured in BAT but still no study has been done about the possible biomarkers for splenic injury. Also biomarkers for the injuries to the diaphragm and biliary system in BAT are also needed to in the future. To recognize these injuries, still we are fully dependent on imaging investigations (Gupta et al. 2004). They are also sometimes recognized during laparotomies (Figs. 3 and 4).

Fig. 3 Avulsed spleen following BAT (courtesy of Dr. Dilip Baral, Department of Surgery, Pokhara Military Hospital, Pokhara, Nepal)

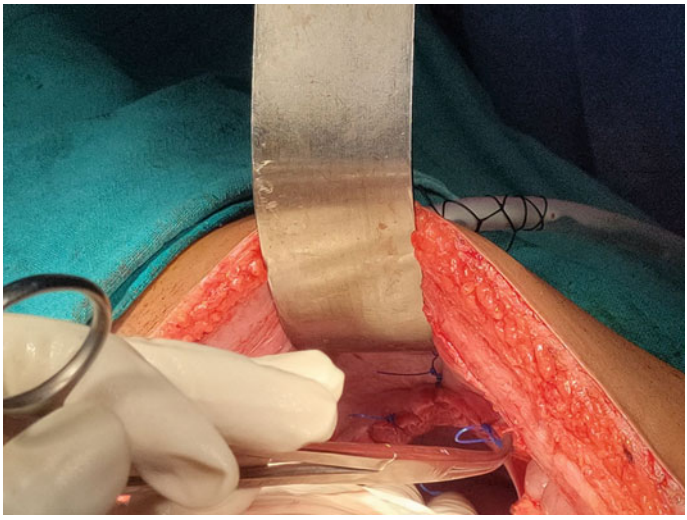

Fig. 4 Repaired diaphragm injury which was due to BAT (courtesy of Dr. Anup Shrestha, Department of Surgery, Indira Gandhi Memorial Hospital, Male, Maldives)

Summary

- The fundamental application of biomarkers can help the modern physician to provide supplementary arsenal in diagnosis and management of BAT.
- AST and ALT may provide valuable aid to the emergency physician to diagnose liver injury and also predict its grade of injury in BAT.
- LDH can be used together with AST and ALT as a complementary test for liver injury in patients with blunt abdominal trauma.
- The biomarkers for kidney injury in BAT are NGAL, KIM-1, IL-18, Cys-C, and renalase. They need to be studied in human population.
- Elevated vs. normal serum amylase and lipase levels showed sole statistically significant association with time elapse since injury to admission, with a cut-off of 3 hours.
- The combination of I-FABP and physical examination may be complementary to each other to rule out hollow viscus injury.
- The serum levels of NLRP3 and HMGB-1 correlates with 6-month mortality in severe BAT patients.
- Reliable studies are needed to be done for CRP to mark as a biomarker for predicting prognosis of patient with BAT.
- High levels of PCT are warranted for aggressive management of BAT to prevent high morbidity and mortality.
- The biomarker for splenic injury, biliary system, and rupture of diaphragm injury due to BAT remains an untouched subject.

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