Splenic injury diagnosis & splenic salvage after trauma

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Chapter 5

Prognostic factors for failure of nonoperative management in adults with blunt splenic injury: a systematic review

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Abstract

Background: Contradictory findings are reported in the literature concerning prognostic factors for failure of non-operative management (NOM) in the treatment of adults with blunt splenic injury. The objective of this systematic review was to identify prognostic factors for failure of NOM, with or without angiography and embolization.

Methods: Medline, Embase, and the Cochrane Library databases were searched. Prospective or retrospective cohort studies addressing failure of nonoperative treatment, with and/or without angiography and embolization, of blunt abdominal injuries were included. Methodological quality of the studies was assessed.

Results: A total of 335 titles and abstracts were screened, of which 31 fulfilled the inclusion criteria. No randomized controlled trials were found. Ten articles were qualified as high-quality articles and used for data extraction (best-evidence synthesis). A total of 25 prognostic factors were investigated, of which 14 were statistically significant in one or more studies. Strong evidence exists that age of 40 years or above, Injury Severity Score (ISS) of 25 or greater, and splenic injury grade of 3 or greater are prognostic factors for failure of NOM. Moderate evidence was found for a splenic Abbreviated Injury Scale of 3 or greater, a Trauma and Injury Severity Score of less than 0.80, the presence of an intraparenchymal contrast blush, as well as transfusion of 1 unit of packed red blood cells or more. Limited evidence was found for large hemoperitoneum, lower Revised Trauma Score, lower Glasgow Coma Scale, lower systolic blood pressure, male sex, the presence of traumatic brain injury, and splenic embolization as protective factor for failure of NOM.

Conclusions: Awareness for failure of NOM is required in patients aged 40 years or older, in patients with an ISS of 25 or higher and those with splenic injury grade 3 or higher. The prognostic factors for failure that we identified should be confirmed in future prospective cohort studies or meta-analyses using individual patient data.

Introduction

Exsanguination caused by abdominal organ injury is one of the main causes of death after trauma.[1] The spleen is the most frequently injured organ in blunt abdominal trauma.[2]

Historically, splenectomy was the treatment of choice for traumatic splenic injury. Presently, non-operative management (NOM, e.g. observation) is the standard of care in haemodynamically stable patients.[3] Angiography and embolization (AE) can be used adjacent to NOM. The greatest advantage of a nonoperative management strategy is preservation of splenic function.

Success rates of NOM of 78 to 98% have been described in the literature.[4-6] The presence of multiple injuries, high grade splenic injury, a large hemoperitoneum, contrast extravasation, age above 55 years, and a high Injury Severity Score (ISS) are patient-related factors frequently reported to be associated with failure of NOM.[7-11] However, data have also been published disputing the increased failure rate in the presence of these factors.[12-16]

Early identification of patients at high risk for failure of NOM is essential since delay in recognition and treatment of late splenic ruptures leads to increased morbidity and mortality.[17, 18] With NOM attempt rates of 90% described in the literature[6], clear parameters in clinical decision aids are of growing importance. In addition, prognostic risk stratification facilitates adequate resource allocation and allows comparison of outcomes between patients and treatment centers.[19-21]

The aim of this study was therefore to systematically review the literature and identify prognostic factors for failure of NOM, with or without AE for patients with blunt splenic injury.

Patients and Methods

Protocol

No protocol existed for this systematic review.

Search Strategy

We performed a literature search identifying studies reporting on prognostic factors for failure of nonoperative treatment. We chose not to narrow down our search terms because some publications consider embolization a separate treatment entity whereas others accept it as part of NOM. MEDLINE, Embase, and the Cochrane library were searched. No lower limit was set for the date of publication.

The literature search was performed with the aid of a clinical librarian according to the Patients, Intervention, Comparison, Outcome (PICO) method.[22] The search strategy is depicted in *Appendix 1*. A manual and cross-reference search was performed, and the column "related citations" in MEDLINE was screened.

Inclusion and Exclusion Criteria

Randomized controlled trials, prospective or retrospective cohort studies, and cross-sectional studies describing prognostic factors for failure of treatment in adults with blunt splenic injury were eligible for inclusion. Prognostic factors were described as factors that can potentially predict the future course subsequent to disease onset.[23]

Case reports or case series, editorial letters or comments, discussions, meeting abstracts, narrative reviews, studies describing (abdominal) organs other than the spleen, studies describing the paediatric population (age < 15 years), animal studies and studies written in a language other then English, French, German, or Dutch were excluded.

Study Selection

Two independent reviewers (C.H.V.D.V. and D.C.O.) simultaneously reviewed titles and abstracts. Articles were included if they compared groups with successful NOM with groups in which NOW failed. After the selection of titles and abstracts, the full text was read to verify if the article met our criteria. Discordance between the reviewers was resolved by discussion.

Risk of Bias

There is no consensus on criteria for assessing methodological quality (currently known as risk of bias) of prognostic studies.[21] We therefore consulted existing checklists and adapted them to our specific study design and subject.[24-27] Since the majority of the included studies were cohort studies, we developed a checklist aimed at this study design. The checklist consisted of six categories (*Appendix 2*). All 17 items on the checklist were equally weighed. One point was assigned if the criterion could be answered with "yes". For "no" and "unclear" no points were rewarded. Studies with a final score of 13 (the 75th percentile) or higher were categorized as high-quality studies. Two reviewers (D.C.O and P.J.) independently assessed risk of bias of all included articles.

Data Extraction

The following features were extracted by two reviewers (D.C.O. and P.J.): risk of bias score, study design, number of included patients, number of patients treated with NOM, definition of NOM and failure of NOM, time to failure, failure rate, relevant information concerning AE, and remarks. Only patient-related prognostic factors that were tested for statistical significance (univariate or multivariate) were used for data extraction.

Best-Evidence Synthesis

We performed a qualitative synthesis of the available evidence (best evidence synthesis[28]) owing to heterogeneity of study characteristics and methodological quality. Subsequently, we only described high-quality studies. Levels of evidence of the identified prognostic factors were categorized using an adapted ordinal scale previously used in other systematic reviews[27, 29] (*Appendix 3*).

Statistical Analysis

Main study characteristics were summarized using descriptive statistics. Pooled failure rate of NOM accounting for interstudy variation was analyzed using a nonlinear random effects model, implemented (PROC NLMIXED) in SAS version 9.1 (SAS Institute Inc., Cary, NC). Statistical uncertainty was expressed in 95% confidence intervals (CIs).

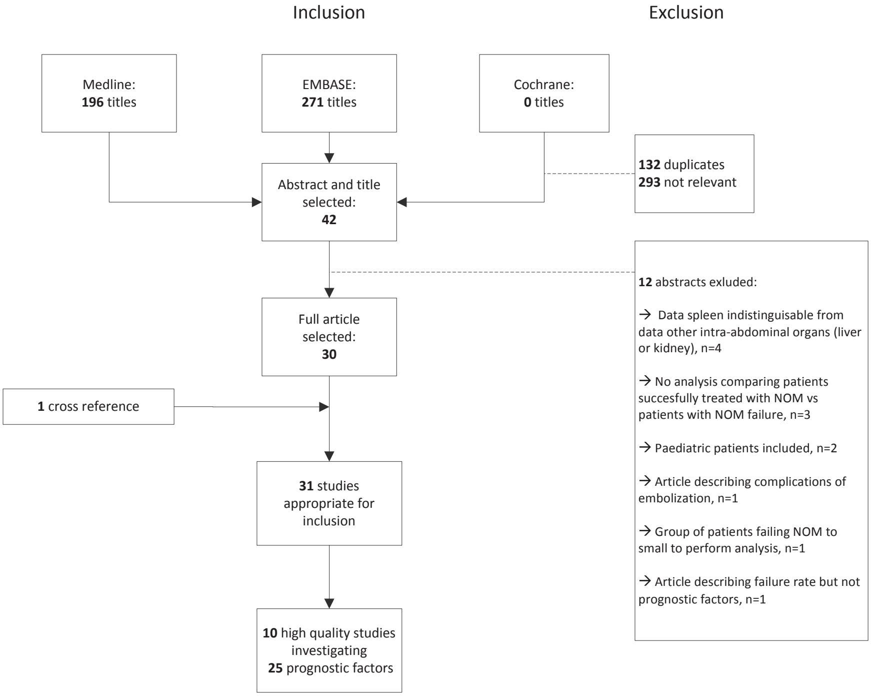
Interobserver agreement for assessing risk of bias was analyzed using an intraclass correlation coefficient (PASW Statistics version 18, SPSS Inc., Chicago, IL). We described the prognostic factors and univariate and multivariate statistics as reported by the authors.

Results

Search Strategy and Study Selection

The search strategy was performed in February 2011 (updated in December 2011). The study selection process is depicted in *Figure 1*. After exclusion of the duplicates (n = 132). After exclusion of the duplicates (n=132), 335 studies were screened, of which 30 met the inclusion criteria. After addition of 1 cross-reference, a total of 31 studies remained.

Figure 1. Overview of the article selection process



Risk of Bias

Median (p25-p75) score for risk of bias was 12 (11-13). Interobserver agreement on risk of bias was good (intraclass correlation coefficient of 0.91; 0.82-0.96). Discordance between observers was observed for twenty studies and was resolved through discussion.

Ten (32%) studies were categorized as high-quality studies. Almost all studies that were not categorized as high-quality lost points on the same three items (*Appendix 2*). There were three items on the checklist (*Appendix 2*) where almost all studies that were not categorized as high quality lost points. In *Table 1* a specification is given per study.

Table 1 - Studies not included in the best evidence synthesis (n=21)

Author, Date	Item on checklist where no points were rewarded																	Final score*
	1 Prospective cohort	2 Splenic injury (AAST)	3 Baseline charac-teristics	4 Conse-cutive inclusion	5 Age ≥ 15 years	6 Defini-tion of NOM	7 Selection criteria	8 Time frame treat-ment	9 Failure of NOM	10 Time frame out-come	11 Drop out rate	12 Prognos-tic factors	13 Outcome is reported	14 Failure rate	15 Freqency or % for prognos-tic factors	16 Analysis (uni or multi-variate)	17 CI presen-ted	
Hashemzadeh et al., 2010	X		X	X	X			X		X		X	X		X	X	X	6
Notash et al., 2007	X		X		X			X		X							X	11
Smith et al., 2007	X			X		X	X		X								X	11
Markogiannakis et al., 2006	X		X		X			X									X	12
Watson et al., 2006	X			X			X			X							X	12
Smith et al., 2006	X			X				X	X	X								12
Haan et al., 2004	X				X			X		X							X	12
Velmahos et al., 2003			X		X	X		X		X							X	11
Malhotra et al., 2003	X				X			X		X		X			X	X	X	9
Albrecht et al., 2002	X			X		X		X									X	12
Halbrecht et al., 2001	X		X	X		X	X	X	X	X							X	8
Bee et al., 2011	X			X	X		X			X								12
Peitzman et al., 2000	X		X	X			X	X									X	11
Cocanour et al., 2000	X	X		X	X										X		X	11
Shapiro et al., 1999	X						X	X		X							X	12
Konstantakos et al., 1999	X				X	X	X	X							X	X	X	9
Sanders et al., 1999	X				X	X		X			X						X	11
Godley et al., 1996	X			X		X		X									X	12
Gavant et al., 1997	X		X	X	X			X			X					X	X	9
Van der Vlies et al., 2011	X			X				X							X	X	X	11
Federle et al, 1998	X		X							X						X	X	12

Best-Evidence Synthesis and Overall Failure Rate

Extracted data of 10 high-quality studies are shown in *Table 2 and Figure 2*. All were cohort studies, nine retrospective (two multicenter) and one prospective. Publication dates ranged from 1995 to 2011. Publication dates ranged from 1995 to 2011. We included two studies by Velmahos et al. which we subsequently named Velmahos included, further called Velmahos 1[30] and Velmahos 2[17]. In half of the ten high quality studies AE was applied. Pooled failure rate of NOM was 18.4% (95% Cl: 11.5 -28.1).

In total, 25 prognostic factors for failure of NOM were tested, of which 14 were statistically significant in one or more studies (only significant factors are presented in the right column of *Figure 2*). Of the 10 studies, 4 performed univariate and multivariate analyses of the data and 6 performed both univariate and multivariate analyses.

Table 2. Results of Included High-Quality Studies (n = 10) on Prognostic Factors for Failure of NOM in Patients With Traumatic Blunt Splenic Injury

Author, publication year	Risk of bias score	Study design (n)	No. patients treated with NOM	Definition of NOM	Definition of failure of NOM	Time to failure	Failure rate n (%)	AE	Remarks
Renzulli et al., 2010	15	RC (206)	159	Not described	The need for a delayed splenectomy	Mean (sd): 6.4 (6.7) Median: 4 (1-26)	16 (10.1%)	AE is considered a separate treatment entity - 11, 9[¤] successful - 1 of the successful AE needed splenectomy on day 4 - 2 undergoing NOM received AE for delayed splenic rupture	Transcatheter arterial embolization was introduced in 2005. (study period 2000-2008)
Barone et al., 1999	13	RC (33)	23	Observation	The need for surgery after observation	Mean 62.5 (9 hours-8 days)	4 (17%)	None	Multicenter study among 7 trauma centers in a single state. Patients that died within 24 hours of hospital admission (n=8) were excluded from further analysis
Velmahos et al., 2010: 1	13	RC (388)	224	Not described	The need for surgery after a trial of NOM	Mean: 2 (3.5) Median: 1 (0-18 days)	85 (38%)	None	Multicenter study among 14 New England trauma centers (11 level 1 and 3 level II)
Velmahos et al., 2000: 2	13	RC (105)	56	Not described	The need for operation due to ongoing bleeding from the spleen in patients managed nonoperatively	Mean ± SD: 29 ± 3 hours	29 (52%)	None	38 patients who died within 48 hours were excluded form analysis

Author, publication year	Risk of bias score	Study design (n)	Nn. patients treated with NOM	Definition of NOM	Definition of failure of NOM	Time to failure	Failure rate n (%)	AE	Remarks
McIntyre et al., 2005	14	RC (2243)	1097 [0]	No splenectomy within 4 hours of presentation to the emergency department	Patients who required splenectomy, splenorrhaphy, or embolization after 4 hours following admission from the emergency department	90 patients: 4-8 h 140 patients: > 8 h → 62 [i] patients: > 48 h	230 (21%)	AE is not considered as NOM. 1 patient in whom NOM failed was embolized within >8-24 hours and 3 patients in whom NOM failed within >24 hours	Splenic injury was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code 865.
Gonzalez et al., 2008	14	RC (190)	107	Observation with or without embolization	The need for surgical exploration after a trial of NOM	Median: 3 (1-15 days)	25 (23,4%)	AE is considered as a NOM strategy. Indication for AE is the presence of a pseudoaneurysm. 2 patients received AE, 1 successfully	Article in French Level of significance P<0.01
Nix et al., 2001	13	RC (542)	407	Not described	Patients who were taken to the operating room for delayed exploration	Age < 55 y: 44.6 (2.5-243) Age > 55 y: 25.8 (3.9-75.7)	33 (8%)	None	
Jeremitsky et. al, 2011	13	RC (499)	477	Not described	The need for splenectomy within 1 hour of admission	78 patients: < 24 hours 5 patients: between 24 to 48 hours 9 patients : >48 hours	70 (14%)	AE is considered an adjunct to NOM. 41 patients were embolized.	

Author, publication year	Risk of bias score	Study design (n)	Nn. patients treated with NOM	Definition of NOM	Definition of failure of NOM	Time to failure	Failure rate n (%)	AE	Remarks
Schurr et al., 1995	14	RC (309)	89	Observation and admission to the intensive care unit	The need for splenectomy or splenorrhaphy in any patient who was initially admitted to the ICU and observed	Average 4 days (1-9)	11‡ (12%)	AE is not considered as NOM. 1 patient (8%) in whom NOM failed was embolized.	According to the definition of failure of NOM, the embolized patient should have underwent splenectomy or splenorrhaphy
Meguid et al., 2005	15	PC (99)	68	NOM protocol consists of a CT scan to document the severity of injury followed by admission to the surgical intensive care unit	Patients initially admitted for NOM who subsequently required laparotomy and splenectomy	3 patients:< 12 hours of admission 2 patients < 24 hours 1 patient: 48-72 hours	8 (12%)	None	

RC: retrospective cohort study; PC: prospective cohort study; AE: angiography & embolization, BSI: blunt splenic injury, SBP: systolic blood pressure; ICU: Intensive Care Unit;*: grade 4 or 5 à operation indication, ¤: there was no contrast medium extravasation in two patients so no embolization was performed, ^{0}: children < 14 years of age were excluded from our analysis. ¡: includes children < age of 14 years. ‡ 1 patient in whom NOM failed received SAE. However, this is beyond their employed definition of NOM and therefore we have withdrawn this patient from the failure group

Figure 2. Investigated prognostic factor(s) for failure of NOM in high quality studies (n=10)

<table>
<tr><th>Author, Publication year</th><th>Investigated prognostic factor(s)</th><th>Identified prognostic factor(s)</th></tr>
<tr><td>Renzulli et al., 2010</td><td>- Age
- Gender (male sex)
- Time that trauma occurred (day vs night)
- Mechanism of injury (traffic vs non-traffic related)
- Setting of primary care (direct admission to level I ED versus initial evaluation at a regional hospital)
- Fluid administration until admission
- ED SBP
- ED mean blood pressure
- Shock index (quotient of cardiac rate and SBP)
- GCS
- (Quantity of) hemoperitoneum
- Isolated or near-isolated splenic injury
- Associated liver injury
- ASA score
- CT splenic injury grade
- RTS
- ISS
- TRISS
- Number of RBC transfusions during the first
- 24 hours after admission</td><td>Univariate and multivariate analysis:
<table>
<tr><th></th><th>Crude OR *(95% CI)</th><th>Adjusted OR *(95% CI)</th></tr>
<tr><td>Age ≥ 40 years</td><td>11.30 (3.12 – 65.51)</td><td>13.58 (2.76 - 66.71)</td></tr>
<tr><td>Large hemoperitoneum +</td><td>3.06 (1.00 – 9.27)</td><td>1.80 (0.47 - 6.86)</td></tr>
<tr><td>CT splenic injury grade ≥ 3</td><td>3.50 (1.08 – 11.37)</td><td>3.38 (0.82 -13.95)</td></tr>
<tr><td>TRISS < 0.80</td><td>3.66 (1.16 – 11.50)</td><td>3.70 (0.99 – 13.86)</td></tr>
</table>
* Logistic regression
+ Defined as: perisplenic blood, blood in Morrison’s pouch, the presence of blood in one or both pericolic gutters and free blood in the pelvis.</td></tr>
<tr><td>Barone et al., 1999</td><td>- Age > 55 years with the following five age categories: 56-59, 60-69, 70-79, 80-89, >90
- ISS</td><td>Univariate analysis:
<table>
<tr><th></th><th>f-NOM vs. s-NOM</th><th>p-value</th></tr>
<tr><td>Age (years)</td><td>60 ± 4 vs. 72 ± 10</td><td>0.01</td></tr>
<tr><td>ISS (points)</td><td>17 vs. 12.4</td><td>0.02</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Author, Publication year</th><th>Investigated prognostic factor(s)</th><th>Identified prognostic factor(s)</th></tr>
<tr><td>Velmahos et al., 2000: 2</td><td>- Age
- ISS
- AIS
- GCS
- SBP
- CT splenic injury grade
- Number of units blood that were transferred during first 24 hours
- Associated intra abdominal injury
- Associated extra abdominal injury</td><td>Univariate analysis:
<table>
<tr><th></th><th>f-NOM vs. s-NOM</th><th>p-value</th></tr>
<tr><td>Age</td><td>37.5 ±13 vs. 26 ± 19</td><td>0.01</td></tr>
<tr><td>ISS</td><td>20 ± 12 vs. 14 ± 9.5</td><td>0.02</td></tr>
<tr><td>Blood transfused in the first 24 hours</td><td>6 ± 4 vs. 0.5 ± 1.0</td><td><0.001</td></tr>
<tr><td>CT splenic injury grade</td><td>3.3 ± 0.9 vs. 2.1 ± 0.9</td><td><0.001</td></tr>
</table>
Multivariate analysis:
<table>
<tr><th></th><th>Adjusted OR *</th></tr>
<tr><td>Transfusion with more than 1 U of blood</td><td>4.6</td></tr>
<tr><td>CT splenic injury grade ≥ 3</td><td>2.5</td></tr>
<tr><td>Abdominal AIS ≥ 3</td><td>Data not presented in article</td></tr>
</table>
* Logistic regression, no confidence intervals presented in article</td></tr>
<tr><td>Velmahos et al., 2010: 1</td><td>- CT splenic injury grade 4 or 5
- Age
- Gender (male sex)
- Type of injury (motor vehicle crash, fall, assault)
- ISS
- SBP on admission
- Heart rate on admission
- Hematocrit on admission
- Brain injury
- Associated intra-abdominal injury
- Major fracture (including pelvic, long bone or spinal fractures)
- Contrast extravasation on CT
- Free blood on CT</td><td>Univariate analysis:
<table>
<tr><th></th><th>f-NOM vs. s-NOM</th><th>p-value</th></tr>
<tr><td>CT splenic injury grade</td><td></td><td>0.009</td></tr>
<tr><td>Grade 4</td><td>67(79) vs. 127 (91)</td><td></td></tr>
<tr><td>Grade 5</td><td>18 (21) vs. 12 (9)</td><td></td></tr>
<tr><td>Presence of brain injury</td><td>13 (15) vs. 9 (6.5)</td><td>0.04</td></tr>
<tr><td>Contrast extravasation</td><td>46 (54) vs. 55 (40)</td><td>0.04</td></tr>
</table>
Multivariate analysis:
<table>
<tr><th></th><th>Adjusted OR * (95% CI)</th></tr>
<tr><td>Grade V BSI</td><td>3.01 (1.36-6.67)</td></tr>
<tr><td>Presence of brain injury</td><td>2.82 (1.14-7.01)</td></tr>
</table>
* Logistic regression</td></tr>
</table>

<table>
<tr><th>Author, Publication year</th><th>Investigated prognostic factor(s)</th><th>Identified prognostic factor(s)</th></tr>
<tr><td>**McIntyre et al., 2005**</td><td>- Trauma's designation level
- Age
- Heart rate on presentation at the ED
- SBP on presentation at the ED
- GCS
- ISS with the following categories: 1-8, 9-16, 17-25 and ≥26
- Associated injury (abdomen and another body region injured, AIS score 2-6)</td><td>Univariate analysis:
<table>
<tr><th></th><th>f-NOM vs. s-NOM</th><th>p-value</th></tr>
<tr><td>ISS > 25</td><td>104 (41.3) vs. 321 (23.3)</td><td><0.001</td></tr>
<tr><td>Age > 55 years</td><td>45 (17.9) vs. 141 (10.2)</td><td><0.01</td></tr>
</table></td></tr>
<tr><td>**Gonzalez et al., 2008**</td><td>- Age
- Gender
- Trauma mechanism
- Heart rate
- SBP at admission
- Haemoglobin level at admission
- Creatinine level at admission
- Splenic injury grade
- Presence of a contrast extravasation or pseudoaneurysm</td><td>Univariate analysis:
<table>
<tr><th></th><th>f-NOM vs. s-NOM</th><th>p-value</th></tr>
<tr><td>Splenic injury grade</td><td>0% for grade I
22.6% for grade II
27.6% for grade III
40% for grade IV</td><td><0.01</td></tr>
<tr><td>Gender M/F</td><td>1.61 vs. 2.4</td><td><0.01</td></tr>
</table></td></tr>
<tr><td>**Nix et al., 2001**</td><td>- Age (above or below 55 years old)
- ISS
- Hemodynamic status at admission
- CT splenic injury grade</td><td>Univariate analysis:
<table>
<tr><th></th><th>f-NOM vs. s-NOM</th><th>p-value</th></tr>
<tr><td>CT splenic injury grade</td><td>3.33 vs. 2.21</td><td><0.001</td></tr>
</table>
Multivariate analysis:
<table>
<tr><th></th><th>Adjusted OR * (95% CI)</th></tr>
<tr><td>Grade 2 and 3 splenic injury</td><td>0.06 (0.02-0.14) *</td></tr>
<tr><td>Grade 4 and 5 splenic injury</td><td>19.2 (7.00-52.62)*</td></tr>
</table>
* Logistic regression</td></tr>
</table>

<table>
<tr><th>Author, Publication year</th><th>Investigated prognostic factor(s)</th><th>Identified prognostic factor(s)</th></tr>
<tr><td>Jeremitsky et al., 2011</td><td>- Age
- Male gender
- White race
- Type of injury
- SBP
- GCS
- ISS
- AIS abdomen/pelvis
- RTS
- TRISS
- Splenic injury grade
- Blood transfusion at the ED
- Co-morbidities
- Splenic embolization</td><td>Univariate analysis:
<table>
<tr><th></th><th>f-NOM vs. s-NOM</th><th>p-value*</th></tr>
<tr><td>SBP</td><td>105.6 ± 36.4 vs. 129.0 ± 26.5</td><td><0.001</td></tr>
<tr><td>GCS</td><td>11.2 ± 5.3 vs. 13.6 ± 3.5</td><td><0.001</td></tr>
<tr><td>ISS</td><td>34.6 ± 13.4 vs. 21.6 ± 11.0</td><td><0.001</td></tr>
<tr><td>AIS abdomen/pelvis</td><td>3.9 ± 0.3 vs. 2.9 ± 0.7</td><td><0.001</td></tr>
<tr><td>RTS</td><td>6.1 ± 2.6 vs. 7.3 ± 1.5</td><td><0.001</td></tr>
<tr><td>TRISS</td><td>0.7 ± 0.4 vs. 0.9 ± 0.2</td><td><0.001</td></tr>
<tr><td>Splenic injury grade</td><td></td><td><0.001</td></tr>
<tr><td>Grade 3</td><td>29 (31.5%) vs. 110 (27%)</td><td></td></tr>
<tr><td>Grade 4</td><td>32 (34.8%) vs. 37 (9.5%)</td><td></td></tr>
<tr><td>Grade 5</td><td>18 (19.6%) vs. 6 (1.5%)</td><td></td></tr>
<tr><td>Blood transfusion at the ED</td><td>46 (50.6%) vs. 37 (9.5%)</td><td><0.001</td></tr>
</table>
Multivariate analysis:
<table>
<tr><th></th><th>Adjusted HR * (95% CI)</th></tr>
<tr><td>Splenic injury grade ≥ 3 ‡</td><td></td></tr>
<tr><td>- Grade III</td><td>5.26 (1.74-15.94)</td></tr>
<tr><td>- Grade IV</td><td>6.84 (2.06-22.74)</td></tr>
<tr><td>- Grade V</td><td>9.81 (2.22-42.96)</td></tr>
<tr><td>Blood transfusion at the ED</td><td>2.66 (1.62-4.37)</td></tr>
<tr><td>AIS abdomen/pelvis</td><td>1.95 (1.29-2.95)</td></tr>
<tr><td>SBP (mmHg)</td><td>0.99 (0.98-0.99)</td></tr>
<tr><td>Splenic embolization</td><td>0.18 (0.06-0.55)</td></tr>
</table>
* Cox Proportional Hazard model (adjusted for age, gender and ethnicity).
‡ grade 1 splenic injury as reference group</td></tr>
</table>

<table>
<tr><th>Author, Publication year</th><th>Investigated prognostic factor(s)</th><th>Identified prognostic factor(s)</th></tr>
<tr><td>Schurr et al., 1995</td><td>- Age
- Heart rate
- SBP
- Hematocrit
- CT splenic injury grade
- Contrast extravasation on CT scan</td><td>Univariate analysis:
<table>
<tr><th></th><th>f-NOM vs. s-NOM</th><th>p-value</th></tr>
<tr><td>Presence of a contrast blush</td><td>8 (80%) vs. 5 (14%)</td><td><0.001</td></tr>
</table>
Multivariate analysis
<table>
<tr><th></th><th>Adjusted OR * (95% CI)</th></tr>
<tr><td>Presence of a contrast blush</td><td>24 (3.90-147.43)</td></tr>
</table>
* Logistic regression</td></tr>
<tr><td>Meguid et al., 2005</td><td>- Age
- Gender
- ISS
- SBP
- Hemoglobin
- Number of transfused RBC
- CT splenic injury grade
- Associated injuries</td><td>None of the prognostic factors were statistically significant in univariate analysis</td></tr>
</table>

ED: emergency department; SBP: systolic blood pressure; GCS: Glasgow Coma Score; ASA: American Society of Anesthesiologists; RTS: revised trauma score, ISS: injury severity score; TRISS: trauma and injury severity score; RBC: red blood cells; AIS: abbreviated injury score; BSI: blunt splenic injury

Values in univariate analysis are provided as number (percentage) for categorical values and as mean (with SD if available) for continuous variables.

Significant prognostic factors for failure of NOM

Age

All 10 studies reported about age. Older age was found to be a significant prognostic factor for failure in four studies.[9,12,17,31] Renzulli et al.[9] demonstrated that a cutoff point at 40 years discriminated best between failure and success in univariate analysis (Odds Ratio [OR], 11.30; 3.12-65.61). This was confirmed in multivariate analysis. Barone et al.[12] investigated a small cohort of patients older than 55 years. Mean (SD) age of successfully observed patients was 72 (10) years, as opposed to 60 (4) years for those who failed observation ($p < 0.01$). Although they concluded that patients with failed observation were significantly younger than patients successfully observed, all patients were older than 55 years. Velmahos 2[17] also demonstrated that patients failing NOM were older (37.5 (13) years vs. 26 (19) years; $p = 0.01$), but only in univariate analysis. McIntyre et al.[31] concluded that patients failing NOM were more likely to be older than 55 years compared with patients successfully treated with NOM ($p < 0.01$).

Sex

Five studies[9, 30, 32-34] reported about the relationship between sex and failure of NOM. One study reported a statistically higher amount of men failing NOM ($p < 0.01$).[32] This effect was only demonstrated in univariate analysis.

Hemoperitoneum

Two studies[9,30] analyzed the effect of a hemoperitoneum on failure of NOM. One study found a significant relation in univariate analysis (OR, 3.06; 95% CI, 1.00-9.27), but significance was not reached in multivariate logistic regression (adjusted OR, 1.80; 95% CI, 0.47-6.86).[9]

American Association for the Surgery of Trauma Splenic Injury Grade

Six[9,17,30, 32, 34, 35] of the eight[9, 17, 30, 32-36] studies demonstrated a significant relationship between the effect of splenic injury grade and failure of NOM. Renzulli et al.[9] found an OR of 3.50 (95% CI, 1.08-11.37) for splenic injury grade of 3 or higher in univariate analysis. This effect was not observed in multivariate analysis. Velmahos 2[17] identified level of splenic injury grade 3 or higher on computed tomography (CT) as independent risk factor for failure as well (adjusted OR, 2.5; 95% CI not presented). Velmahos 1[30] analyzed failure rate for patients with Grade IV or V injury. In univariate ($p = 0.009$) and multivariate analysis (adjusted OR, 3.01; 95% CI, 1.36-6.67), Grade V splenic injury was identified as predictor for failure. Gonzalez et al.[32] observed a significantly higher failure rate with increasing grade of splenic injury in univariate analysis ($p < 0.01$). Jeremitsky et al.[34] demonstrated that splenic injury grade of 3 or higher was significantly associated with failure through univariate and multivariate analyses. Nix et al.[35] compared Grade 2 and 3 injuries ("lower grade") with grade 4 and 5 ("higher grade") in multivariate regression analysis. Higher-grade splenic injuries (adjusted OR, 19.2; 95% CI 7.00-52.62) showed a significantly higher risk of NOM failure compared with lower grade-injuries (adjusted OR, 0.06; 95% CI 0.02-0.14).

Abbreviated Injury Scale Abdomen

Two studies reported about abdominal Abbreviated Injury Scale (AIS) score[17 34]. In the study of Velmahos 2,[17] AIS score of 3 or greater was identified as independent risk factor for failure of NOM (no data presented in the study). Jeremitsky et al.[34] demonstrated a mean (SD) AIS score of the abdomen/pelvis of 3.9 (0.3) for patients failing NOM versus 2.9 (0.7) for patients treated successfully ($p < 0.001$). This was confirmed in a Cox regression model (adjusted hazard ratio 1.95; 95% CI, 1.29-2.95).

ISS

Four[12,17,31,34] of the eight[9,12,17,30,31,33-35] studies analyzing ISS found it to be a prognostic factor for failure of NOM. Barone et al. studied the effect of ISS on failure of NOM for patients older than 55 years.[12] The differences in ISS between patients failing observation and successfully observed patients was significant ($p = 0.02$). Velmahos 2[17] observed higher mean ISSs for patients failing NOM as well ($p = 0.02$). ISS of 25 or higher was statistically significant in univariate but not in multivariate analysis. Results of the univariate analysis of McIntyre et al.[31] demonstrated that patients who failed NOM were more likely to have an ISS of greater than 25 ($p < 0.001$). Jeremitsky et al. demonstrated that patients failing NOM had significant higher ISS compared with patients with successful NOM through univariate analysis ($p < 0.001$).[34]

Revised Trauma Score

Two[9,34] studies investigated the relationship between Revised Trauma Score (RTS) and outcome of NOM. Jeremitsky et al.[34] observed a significantly lower

RTS for patients failing NOM compared with patients with successful NOM ($p < 0.001$). Multivariate analysis did not show a significant relation.

TRISS

Both studies[9,34]analyzing the Trauma and Injury Severity Score (TRISS) found a significant association with failure of NOM. Renzulli et al.[9] demonstrated that TRISS of less than 0.80 was a prognostic factor in univariate analysis (OR, 3.66; 95% CI, 1.16-11.50). Borderline significance was reached in multivariable analysis, but the authors stated that TRISS of less than 0.80 did not significantly effect failure rate. Jeremitsky et al. observed a mean (SD) TRISS of 0.7 (0.4) for patients in whom NOM failed compared with 0.9 (0.2) in successful NOM ($p < 0.001$) but could not confirm this finding in a multivariate model.[34]

Glasgow Coma Scale (GCS)

One[34] of the four articles [9,30,31,34] that reported on Glasgow Coma Scale (GCS) found a significant association with failure. Jeremitsky et al.[34] demonstrated that patients failing NOM had a mean (SD) GCS score of 11.2 (5.3) compared with 13.6 (3.5) for patients with successful NOM ($p < 0.001$). This was not demonstrated in multivariate analysis.

Systolic Blood Pressure

Systolic Blood Pressure (SBP) was analyzed in eight studies[9,17,30,31-34,36]. One study reported that patients in whom NOM failed had significantly lower admission SBP, confirmed by multivariate analysis (adjusted HR, 0.99; 95% CI, 0.90-0.99).[34]

Traumatic Brain Injury

One multicenter study found a significant relationship between the effect of traumatic brain injury and failure of NOM in univariate ($p = 0.04$) and multivariate analysis (adjusted OR, 2.82; 95% CI, 1.14-7.01.[30]

Contrast Extravasation

Contrast extravasation on CT, defined as a hyperdense collection of contrast media in the splenic parenchyma, was identified as prognostic factor for failure of NOM by two of the three[30,32,36] studies investigating this factor. Velmahos 1[30] stated that contrast extravasation is more frequently present in patients failing NOM compared with patients with successful NOM ($p = 0.04$). This could not be confirmed through multivariate analysis. Schurr et al.[36] estimated that a patient is 24 times more likely to fail NOM when contrast extravasation is present compared with patients without contrast extravasation (adjusted OR, 24; 95% CI, 3.90- 147.43).

Number of Transfused Packed Red Blood Cell Units

Two[17,34]out of four [9,17,33,34] studies demonstrated a significant relationship between failure of NOM and the number of transfused red blood cells (RBCs) units. According to Velmahos 2,[17] patients with failed NOM received significantly more units of blood while managed nonoperatively compared with patients with successful NOM ($p < 0.001$). They identified transfusion of more than 1 U of blood as independent risk factor for failure of NOM in logistic regression analysis (HR, 2.66; 95% CI, 1.62-4.37). Jeremitsky et al.[34] concluded that patients who failed NOM were more likely to require blood transfusions compared with those with successful NOM in univariate ($p < 0.001$) and multivariate analyses (adjusted HR, 2.66; 95% CI, 1.62-4.37).

Splenic embolization

Jeremitsky et al.[34] analyzed the effect of splenic embolization on failure of NOM. Multivariate analysis demonstrated that embolization was associated with a decreased risk for failure after adjusting for age, sex, race, blood transfusion at the emergency department, AIS score, history of substance use, and SBP at admission (adjusted HR, 0.18; 95% CI, 0.06-0.55).

Levels of evidence of the identified prognostic factors

Strong evidence exists that age above 40 years old, an ISS of 25 or higher, and splenic injury grade 3 or greater are prognostic factors for failure of NOM. Moderate evidence was available for abdominal AIS score of 3 or greater, TRISS of less than 0.80, the presence of an intraparenchymal contrast blush, and transfusion of more than 1 U of blood. Limited or no evidence was found for the remaining identified prognostic factors (*Table 3*).

Table 3. Levels of evidence on prognostic factors for failure of NOM in patients with traumatic blunt splenic injury

Level of evidence	Prognostic factor
Strong evidence	Age ≥ 40 y
	ISS ≥ 25
	Splenic injury grade ≥ 3
Moderate evidence	Abdominal AIS score ≥ 3
	TRISS < 0.80
	Intraparenchymal contrast blush
	Transfusion of > 1 U of blood
Limited evidence	Splenic embolization*
	Lowered GCS score
	Large hemoperitoneum
	Lower RTS
	Male sex
	Lower admission SBP
	Traumatic brain injury
No evidence	Heart rate
	Shock index
	Haemodynamic status on admission
	Emergency department mean blood pressure
	Fluid administration until admission
	ASA score
	Hemoglobin level
	Hematocrit level
	Creatinine level on admission
	Isolated or near isolated splenic injury
	Associated injury
	Comorbidities

*Protective effect against failure of NOM.
ASA, American Society of Anesthesiologists

Discussion

The present study systematically reviewed literature on prognostic factors for failure of NOM (observation). Of the 31 included studies, 10 were qualified as high quality. Twenty five prognostic factors were investigated, and 14 were found to significantly affect outcome of NOM. These prognostic factors may assist in the early identification of patients at high risk for failure of NOM, preventing delays in recognition and treatment of late splenic ruptures, which are known to lead to increased resource use, morbidity and mortality.[17, 18]

Based on the available evidence, we recommend awareness for failure of NOM in patients aged 40 years or older, patients with splenic injury grade 3 or higher, and patients with an ISS of 25 or higher. Abdominal AIS score of 3 or greater, TRISS of less than 0.80, the presence of an intraparenchymal contrast blush, and an increased transfusion need should a physician to possible failure as well. In the meta-analysis of Bhangu et al.,[18] older age (≥55 years) and higher grade (American Association for the Surgery of Trauma Grades 4 or 5) splenic injuries were also identified as predictors for failure. Bhangu et al.[18] additionally identified moderate or large hemoperitoneum as an independent risk factor for failure, although we found only limited evidence for this factor. After Bhangu et al.[18] performed sensitivity analysis of the high-quality studies, higher-grade splenic injuries and the presence of a moderate/large hemoperitoneum remained significantly associated with failure. However, they solely reviewed English language literature and conclusions of their meta-analysis are based on only four studies.

A substantial number of included studies consider failure of NOM to be an indication for surgery although a splenectomy for trauma is associated with an increased risk of early infectious complications.[37] Surgery no longer is the only available treatment option in case of failure of NOM. Embolization could be attempted if the patient status allows this approach.

Our study was severely limited by the quality of the available studies. No prospective randomized studies were identified, and only one prospective cohort study was available. Another limitation was the amount of heterogeneity throughout the studies: different definitions and cutoff values were used, and study results were based on different sets of prognostic factors, different methods of statistical analysis, and different levels of significance.

Another limitation is the translation of a dichotomous outcome to the clinical situation. Should a 41-year-old patient be treated in the same way as a 91-year-old? Although age over 40 years is found to be the best discriminator between success and failure of NOM in the study of Renzulli et al.,[9] age over 50 and age over 60 years (OR of 5.78 and 2.32, respectively) were identified as discriminators as well. We think that patients older than 40 years can be managed nonoperatively, but we would like to create awareness for possible failure of NOM in this specific age group.

The strength of this review lies in the summary of prognostic factors significantly associated with failure of NOM according to the best evidence. We attempt to offer the physician some practical cutoff points to facilitate the decision-making process. The prognostic factors identified in this review should be confirmed on a large-scale prospective cohort study or in a meta-analysis using individual patient data (IPD) to strengthen the conclusions drawn from this review. IPD reuiqres the gathering of original patient data from original studies and can improve the quality of the data, the analyses, and the reliability of the results.[38] To perform IPD, all authors that published about a topic should be willing to share their data. In addition, unpublished data should be collected. However, this poses a significant challenge.[39]

Conclusion

Awareness for failure of NOM is required in patients aged 40 years or older, in patients with an ISS of 25 or higher or those with splenic injury grade 3 or higher. The prognostic factors for failure that we identified should be confirmed in future prospective cohort studies or meta-analyses using IPD.

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Appendix 1.

Detailed Search Strategy Databases MEDLINE and Embase

MEDLINE	EMBASE
((angioembolization OR angio-embolization OR angioembolisation OR angio-embolisation OR angiography OR embolisation OR embolization OR nonoperative management OR non-operative management) AND ((blunt AND spleen AND injur*) OR blunt splenic injury OR blunt spleen injury OR blunt spleen trauma OR blunt splenic trauma OR blunt abdominal trauma OR blunt abdominal injury OR blunt abdominal solid organ trauma OR blunt abdominal solid organ injury OR (nonpenetrating wound AND (spleen OR splenic OR abdominal)))) AND (treatment failure OR failure OR fail*).	1. abdominal injury/ or abdominal blunt trauma/ or spleen injury/ 2. embolization.tw. 3. 1 and 2 4. artificial embolism/ 5. embolisation.tw. 6. angioembolization.tw. 7. angio-embolization.tw. 8. angioembolisation.tw. 9. angio-embolisation.tw. 10. exp SPLEEN ANGIOGRAPHY/ or exp ABDOMINAL ANGIOGRAPHY/ 11. non-operative management.tw. 12. nonoperative management.tw. 13. conservative treatment/ or bed rest/ or watchful waiting/ 14. 2 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 15. 1 and 14 16. (blunt.tw. and (abdominal injury/ or abdominal trauma.tw. or splenic injury.tw. or spleen trauma.tw. or splenic trauma.tw. or spleen injury/)) or abdominal blunt trauma/ 17. 14 and 16 18. treatment outcome/ or treatment failure/ 19. fail$.tw. 20. fail*.tw. 21. 18 or 20 22. 17 and 21

*Since no articles with our study subject were found in the Cochrane Librabry, the search strategy has not been specified

Appendix 2.

Risk of Bias Checklist Regarding the Systematic Review of Prognostic Factors Associated with Failure of Nonoperative Management of Patients With Blunt Splenic Injury

Study Design

I. Prospective cohort design investigating prognostic factors associated with failure of nonoperative management for patients with traumatic Splenic Injury

Study Population

Description of inclusion (II-IV) and exclusion criteria (V):

II. Patients with splenic injury (diagnosed according to the American Association for the Surgery of Trauma splenic injury scale or a similar grading system) after a blunt trauma mechanism
III. Description of demographic and clinical baseline details (e.g. age, ISS, male-female ratio, admission SBP, admission pulse rate) of the patient group
IV. Consecutive inclusion of patients
V. Age of the included patients 15 years or older*

Treatment

- VI. Definition of NOM (with or without AE) is reported
- VII. Selection criteria for treatment (choice)/ management are reported
- VIII. Time frame to treatment (choice)/ management is reported

Outcome Measurement

- IX. Definition of the primary outcome measurement, failure of NOM, is reported
- X. Time frame of outcome assessment is reported
- XI. Drop out rate less than 10%

Prognostic Factors

- XII. Fully defined (including details of measurement methods if necessary) and include at least one of the following patient relevant prognostic factors: multiple injuries, splenic injury grade, large hemoperitoneum, contrast extravasation, age, ISS, and haemodynamic instability

Data Presentation and Analysis

- XIII. Outcome of all individuals (treated nonoperatively) of the cohort study is reported
- XIV. Failure rate (frequency, percentage or median [CI, Range]) of NOM is reported
- XV. Frequency, percentage, mean or median (SD, CI, Range) are described for at least one of the following patient related prognostic factors: multiple injuries, splenic injury grade, large hemoperitoneum, contrast extravasation, age, ISS, and haemodynamic instability.

The statistical approach is appropriate for the type of data

- XVI. Univariate and/or multivariate analysis is performed
- XVII. If univariate analysis is performed, the univariate estimates or CIs are presented. If multivariate analysis is performed, the suitable multivariate techniques should be used to adjust for other prognostic factors, and there should be an adequate number of events (*N*) in relation to the number of prognostic factors (*K*); at least *N:K* = 10:1

* All articles scored 1 point on this item since age less than 15 years was an exclusion criterion.

Appendix 3.

Adapted Format of Levels of Evidence in Qualitative Data Analysis

Level of evidence	Description
Strong evidence	Generally consistent findings in 3 or more high-quality cohort studies
Moderate evidence	Generally consisting findings in 2 high-quality cohort studies
Limited evidence	(Generally consistent) findings in 1 high-quality cohort study
Conflicting	Conflicting findings in high-quality studies
No evidence	No high-quality studies could be found