swiss medical weekly

**Systematic review** | Published 17 May 2023 | doi:https://doi.org/10.57187/smw.2023.40081
**Cite this as:** Swiss Med Wkly. 2023;153:40081

# Splenic rupture or infarction associated with Epstein-Barr virus infectious mononucleosis: a systematic literature review

**Johannes M. A. Toti[a*], Beatrice Gatti[b*], Isabella Hunjan[b], Lisa Kottanattu[cd], Pietro B. Faré[e], Samuele Renzi[fg], Mario G. Bianchetti[bd], Gregorio P. Milani[hi], Sebastiano A. G. Lava[jk], Pietro Camozzi[l]**

[a] Department of Surgery & Transplantation, University Hospital Zurich Zurich, Switzerland
[b] Family medicine, Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland
[c] Pediatric Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland
[d] Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland
[e] Clinic of Hematology, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland
[f] Division of Hematology and Oncology, CHUL-Laval, Quebec City, Canada
[g] Department of Pediatrics, Laval University, Quebec City, Canada
[h] Pediatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[i] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy
[j] Pediatric Cardiology Unit, Department of Pediatrics, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland
[k] Heart Failure and Transplantation, Department of Pediatric Cardiology, Great Ormond Street Hospital, London, United Kingdom
[l] Department of Anesthesia, Valais Hospital, Switzerland

[*] Equally contributed as co-first authors.

## Summary

BACKGROUND: Epstein-Barr virus (EBV), also known as human herpesvirus 4, is one of the most common pathogenic viruses in humans. EBV mononucleosis always involves the spleen and as such it predisposes to splenic rupture, often without a trauma, and splenic infarction. Nowadays the goal of management is to preserve the spleen, thereby eliminating the risk of post-splenectomy infections.

METHODS: To characterise these complications and their management, we performed a systematic review (PROSPERO CRD42022370268) following PRISMA guidelines in three databases: Excerpta Medica, the United States National Library of Medicine, and Web of Science. Articles listed in Google Scholar were also considered. Eligible articles were those describing splenic rupture or infarction in subjects with Epstein-Barr virus mononucleosis.

RESULTS: In the literature, we found 171 articles published since 1970, documenting 186 cases with splenic rupture and 29 with infarction. Both conditions predominantly occurred in males, 60% and 70% respectively. Splenic rupture was preceded by a trauma in 17 (9.1%) cases. Approximately 80% (n = 139) of cases occurred within three weeks of the onset of mononucleosis symptoms. A correlation was found between the World Society of Emergency Surgery splenic rupture score, which was retrospectively calculated, and surgical management: splenectomy in 84% (n = 44) of cases with a severe score and in 58% (n = 70) of cases with a moderate or minor score (p = 0.001). The mortality rate of splenic rupture was 4.8% (n = 9). In splenic infarction, an underlying haematological condition was observed in 21% (n = 6) of cases. The treatment of splenic infarction was always conservative without any fatal outcomes.

CONCLUSIONS: Similarly to traumatic splenic rupture, splenic preservation is increasingly common in the management of mononucleosis-associated cases as well. This complication is still occasionally fatal. Splenic infarction often occurs in subjects with a pre-existing haematological condition.

Dr Sebastiano A.G. Lava, MD MSc
Pediatric Cardiology Unit
Centre Hospitalier Universitaire Vaudois and University of Lausanne
CH-1011 Lausanne
webmaster[at]sebastianolava.ch

## Introduction

Epstein-Barr virus, also known as herpesvirus 4, is one of the most common human viruses [1, 2]. Primary infectious mononucleosis, the best-known presentation of this virus, typically affects adolescents and young adults; presents with fatigue, malaise, sore throat and enlarged cervical lymph nodes, liver or spleen; and generally spontaneously resolves over a few weeks [1, 2].

The spleen is always involved in mononucleosis. Although not always palpable, splenomegaly is detected by ultrasound in all affected individuals [1–3]. The splenic architecture is distorted because the parenchyma is infiltrated by atypical lymphocytes that compromise the fibrous support system and thin the capsule. Splenomegaly and the distorted architecture predispose to rupture, which is often not associated with a notable trauma but perhaps exclusively heralded by triggers such as coughing, sneezing, straining during defecation or muscular exertion [1, 2, 4]. It is also traditionally assumed that rupture may result from vigorous palpation [4]. There might be an increased tendency to splenic infarction as well [5].

Surgical spleen removal has been the traditional management of both traumatic and atraumatic splenic injury [6–8].

However, since spleen removal may result in immune deficiency and invasive infections due to encapsulated bacteria, which occur especially in children and teenagers [6–9], strategies to conserve splenic function by avoiding total splenectomy have been increasingly proposed [6–9].

The features of mononucleosis-associated splenic rupture and infarction have not been comprehensively investigated in the recent past. Furthermore, it is currently unclear whether spleen-preserving management is considered a viable alternative to splenectomy.

Since mononucleosis-associated splenic rupture and infarction are rare, available knowledge on these complications is mainly based on case reports. To address these issues, we carried out a systematic review of the literature.

## Methods

### Data sources and search strategy

This review was pre-registered in the Prospective Register of Systematic Reviews (PROSPERO; CRD42022370268) and carried out in agreement with the second edition of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [10]. Data sources included Excerpta Medica, the United States National Library of Medicine, and Web of Science from 1 January 1970, without any further limitation. The search strategy incorporated the following terms entered in separate pairs: (Epstein-Barr virus OR glandular fever OR infectious mononucleosis OR herpesvirus 4) AND (hematoperitoneum OR splenic hematoma OR splenic infarction OR splenic rupture). Articles listed within reference lists of the retrieved records, reports published in Google Scholar and articles already known to the authors were also considered. Searches were conducted in April 2022 and repeated before article submission.

### Inclusion criteria

Patients had to meet three criteria to be included: (i) an individually documented case who presented with a positive Paul-Bunnell-Davidsohn test, a specific acute Epstein-Barr virus serology response or both [1, 2]; (ii) having clinical features of primary mononucleosis; and (iii) either a splenic rupture or a splenic infarction. Cases with splenic rupture or infarction not supported by serological evidence of an existing Epstein-Barr virus infection were excluded.

### Data extraction

For each case, the following information was extracted in a pilot-tested spreadsheet: (a) relevant past and recent medical history with emphasis on any pre-existing haematological diseases, recent abdominal trauma or vigorous abdominal palpation; (b) the clinical features of mononucleosis [1, 2], i.e. fever (38.0 °C or more), fatigue, malaise, sore throat, yellowish scleral discolouration (referred to as “jaundice” in the remainder of this article), cervical adenopathy (lymph nodes felt to be 1 cm or larger in diameter), hepatomegaly or splenomegaly (a palpable liver edge or spleen); and (c) clinical and laboratory features of splenic rupture or infarction at presentation, including blood pressure, heart rate and signs of haemodynamic instability (shortness of breath, prolonged capillary refill time, mottling of cool and moist extremities, peripheral cyanosis, altered mentation), pain (classified as diffuse abdominal pain, left upper abdominal pain or left shoulder pain), a full blood count (with leucocyte differential) [11], enzyme values (aminotransferases and lactate dehydrogenase) and imaging studies.

The diagnosis of splenic rupture or splenic infarction was suspected clinically and always confirmed by means of appropriate imaging studies or, in haemodynamically unstable cases, a diagnostic laparotomy. The time elapsed from onset of symptoms of mononucleosis to the diagnosis of splenic rupture or infarction was recorded. The diagnosis of mild mononucleosis was made in cases with two or fewer of the following five typical features: cervical adenopathy, fever, malaise, sore throat, splenomegaly. The diagnosis of mononucleosis-associated transaminitis was made in cases with a more than 2-fold elevation in aminotransferase ratio compared to the laboratory’s reference value. It has been speculated that in mononucleosis a more than 2-fold elevation in lactate dehydrogenase ratio indicates splenic infarction [5]. Consequently, the value of the latter test was verified. Cases with a platelet count of 20–70 × $10^9$/l or <20 × $10^9$/l were recorded.

The clinical and imaging data of each case of mononucleosis-associated splenic rupture was used to score the rupture as minor, moderate or severe according to the spleen trauma classification recommended in 2017 by the World Society of Emergency Surgery (WSES) [12]. This classification takes into account both the anatomy of splenic lesions and the patient’s haemodynamic condition and has proved to be a reliable tool in the decision-making process in splenic trauma treatment [12]. The management was stratified using the following well-established terminology [6–8]: “operative management” was used for cases of splenic rupture who underwent an immediate surgical splenectomy; “failure of non-operative management ” for cases who underwent a surgical splenectomy after an initial unsuccessful conservative approach; “non-operative management” for the remaining patients — this term was used both for cases with conservative care alone and for cases with an adjunctive treatment such as transcatheter arterial embolisation.

### Comprehensiveness of reporting

The comprehensiveness of included cases was evaluated using the following seven components: 1. Characterisation of the patient; 2. Clinical presentation; 3. Disease duration; 4. Vital parameters; 5. Full blood count; 6. Haemodynamic instability; 7. Management and outcome. Each component was rated as 0, 1 or 2 and the reporting quality was graded according to the sum of each item as satisfactory, good or excellent [13].

Two authors (JMAT/BG) separately and in duplicate performed the literature search, selected studies for inclusion, extracted data and evaluated the comprehensiveness of each case. Any disagreements were discussed, and a senior author (MGB) was consulted to resolve any outstanding issues. One author (JMAT) entered the data into a pre-defined worksheet and another (BG) verified the accuracy of data entry.

### Analysis

Pairwise deletion was used to handle missing data. Categorical variables are presented as proportions and continuous variables as medians with interquartile range. Dichotomous categorical variables were compared using the Fisher exact test; ordered categorical variables using the Kruskal-Wallis test and the post-hoc Tukey correction; and continuous variables using the Mann-Whitney-Wilcoxon rank-sum test. Linear regressions with the Spearman nonparametric coefficient of correlation $r_s$ were also calculated. A two-sided significance level of 0.05 was used. GraphPad Prism 9.5.1 (GraphPad Software, San Diego, California, USA) was used for statistics.

### Ethics approval and consent

The study was a systematic review and as such did not require specific ethics approval at our institutions.

## Results

### Search results

The analysis included 171 articles published between 1970 and 2022 [14–184] (figure 1). The languages of these 171 reports were English (130), Spanish (19), German (12), French (6) and Italian (4). The reports originated from the following continents (countries): 86 from Europe (United Kingdom: 23, Spain: 15, Germany: 13, Italy: 7, Switzerland: 7, France: 6, Belgium: 5, Greece: 3, Ireland: 2, Netherlands: 2, Portugal: 2, Czechia: 1), 62 from the Americas (United States of America: 55, Canada: 3, Chile: 2, Mexico:1, Peru: 1), 17 from Asia (Japan: 5, Israel: 3, South Korea: 3, India: 2, China: 2, Pakistan: 1, Saudi Arabia: 1) and 6 from Oceania (Australia: 5, New Zealand: 1). The 171 reports addressed cases of mononucleosis complicated by splenic rupture (144 reports), cases complicated either by rupture or infarction (1) or cases complicated by infarction (26). The reports documented 215 patients (one patient in 148 reports, two patients in 11 reports, three patients in 7 reports, four patients in 4 reports and eight patients in 1 report): 186 with splenic rupture [14–158] and 29 with infarction [158–184]. Reporting comprehensiveness was satisfactory in 1 case, good in 125 and excellent in 89.

### General findings

The characteristics of the 215 patients are presented in table 1. A positive Paul-Bunnell-Davidsohn test (n = 90), a specific acute Epstein-Barr virus serology response (n = 87) or both a Paul-Bunnell-Davidsohn test and a specific Epstein-Barr virus serology response (n = 30) supported the diagnosis of mononucleosis in 207 cases. The diagnosis of mononucleosis was made uniquely on a histological basis (spleen showing largenumbers of atypical lymphocytes) in the remaining 8 cases, who died within hours after admission. A pre-existing haematological disease was significantly more frequent (p = 0.001) in splenic infarction as compared to splenic rupture. The prevalence of recent history of abdominal trauma was not statistically different between rupture and infarction patients. In no cases was rupture or infarction preceded by overeager palpation. As compared to cases affected by splenic infarction, cases with splenic rupture presented less frequently with fever or fatigue (table 1). Furthermore, left shoulder pain and haemodynamic instability were more frequent in the splenic rupture group (p = 0.001). A transaminitis was significantly more common in the splenic infarction group (p = 0.001). The prevalence of cases with lactatedehydrogenase level ≥600 U/l was similar in patients with splenic rupture and in those with splenic infarction. The tendency towards a platelet count 20–70 × $10^9$/l or <20 × $10^9$/l was not statistically different in the two study groups.

Information on the elapsed time between onset of mononucleosis symptoms and signs of splenic disease was available for 145 cases with rupture (54 females and 91 males; 20 [17–25] years) and 26 cases with infarction (8 females and 18 males; 19 [17–20] years) (figure 2). At least 80% of all cases occurred within three weeks after the onset of mononucleosis symptoms. The mentioned time interval was on average slightly but significantly longer for rupture than for infarction (8 [6–14] vs 7 [4–10] days; p = 0.034). In approximately 10% of cases, the splenic disease occurred four weeks or more after the clinical presentation of mononucleosis.

### Splenic rupture

The relationship between the World Society of Emergency Surgery splenic rupture score and management in patients with splenic rupture is shown in table 2. While almost 85% of cases with a severe rupture score were splenectomised, this figure was about 50% for cases with a minor or moderate rupture score (p = 0.001).

The severity of splenic rupture and its management were analysed over five periods: 1970–1979, 1980–1989, 1990–1999, 2000–2009 and 2010–2022 (figure 3). The

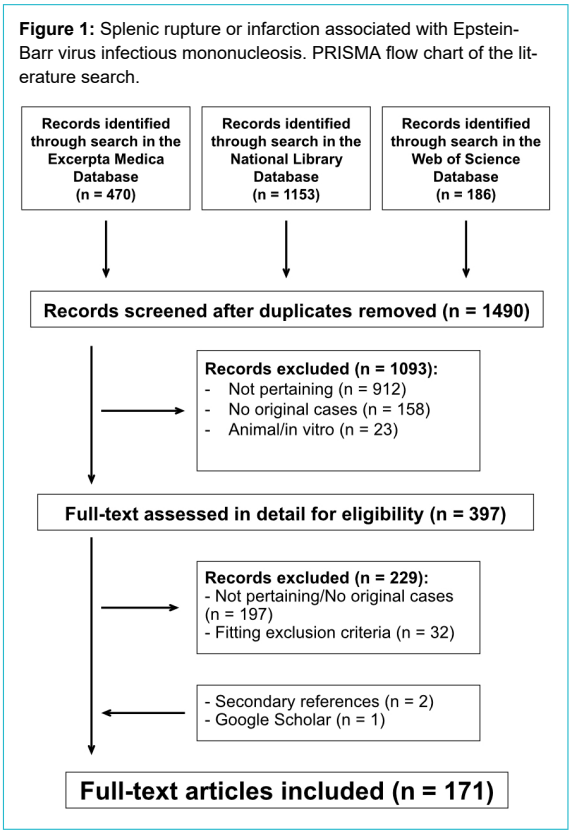



**Figure 1:** Splenic rupture or infarction associated with Epstein-Barr virus infectious mononucleosis. PRISMA flow chart of the literature search.

splenic rupture was classified as minor in 52 (30%), moderate in 66 (38%) and severe in 58 (33%) of the 176 cases with this information. The splenic rupture classification score was not statistically different in the five periods (p = 0.415).

Splenectomy, either immediate (operative management; n = 108) or after failure of non-operative (failure of operative management; n = 15) management was the most common treatment strategy. In the remaining 63 patients, the management was non-operative: expectant strategy alone (n = 52), transcatheter embolisation (n = 5), partial splenectomy (n = 2), splenic repair (n = 2) and ultrasound-guided haematoma aspiration (n = 2). The prevalence of cases managed non-operatively significantly (p = 0.0134) increased over the five periods: while no case was managed non-operatively in 1970–1979, this strategy was successfully applied in slightly less than 50% of cases in 2010–2022 (figure 3).

Nine patients with a severe splenic rupture score (6 female and 3 male subjects aged 15 to 29 years, median 20 years)

**Table 1:**
Characteristics of 215 patients (82 females and 133 males) with Epstein-Barr virus mononucleosis complicated by splenic rupture or infarction. Results are presented as frequency (and percentage) or as median (with interquartile range). Significant p values are given in bold.

| | | | Splenic rupture | Splenic infarction | p value |
|---|---|---|---|---|---|
| n | | | 186 | 29 | |
| Females:Males, n (%) | | | 73 (40): 113 (60) | 9 (30): 20 (70) | 0.538 |
| Age | Years | | 20 [17–25] | 19 [17–22] | 0.136 |
| | <16 years, n (%) | | 17 (9.1) | 5 (17) | 0.189 |
| Pre-existing haematological disease, n (%) | | | 1 (0.5) | 6 (21) | **0.001** |
| History | Fever, n (%) | | 95 (51) | 26 (90) | **0.001** |
| | Malaise, n (%) | | 107 (58) | 16 (55) | 0.842 |
| | Fatigue, n (%) | | 40 (22) | 13 (45) | **0.010** |
| | Sore throat, n (%) | | 99 (53) | 21 (72) | 0.070 |
| | Nausea, vomiting, diarrhoea n (%) | | 51 (27) | 11 (38) | 0.273 |
| | Previous abdominal trauma*, n (%) | | 17 (9.1) | 0 (0) | 0.137 |
| | Vigorous abdominal palpation, n (%) | | 0 (0) | 0 (0) | 0.999 |
| Examination | Abdominal pain | No abdominal pain, n (%) | 14 (7.5) | 2 (6.9) | 0.999 |
| | | Diffuse abdominal pain, n (%) | 172 (93) | 27 (93) | 0.904 |
| | | Left upper quadrant pain, n (%) | 112 (60) | 19 (66) | 0.684 |
| | Left shoulder pain, n (%) | | 68 (37) | 2 (6.9) | **0.001** |
| | Enlarged cervical lymph nodes, n (%) | | 97 (52) | 13 (45) | 0.550 |
| | Jaundice, n (%) | | 8 (4.3) | 8 (28) | **0.001** |
| | Hepatomegaly, n (%) | | 25 (13) | 8 (28) | 0.091 |
| | Splenomegaly, n (%) | | 152 (83) | 25 (86) | 0.794 |
| Mild presentation, n (%) | | | 38 (20) | 1 (3.4) | **0.035** |
| Haemodynamic parameters | Heart rate, bpm | | 105 [90–122] | 105 [86–115] | 0.887 |
| | Systolic blood pressure, mm Hg | | 102 [90–115] | 126 [115–130] | **0.009** |
| | Diastolic blood pressure, mm Hg | | 60 [53–70] | 70 [64–81] | **0.034** |
| | Haemodynamic instability, n (%) | | 58 (31) | 0 (0) | **0.001** |
| Laboratory findings | Haemoglobin (g/l) | | 105 [90–122] | 123 [78–134] | 0.425 |
| | Platelet count | $10^9$/l | 170 [101–230] | 190 [135–309] | 0.290 |
| | | <20 × $10^9$/l, n (%) | 3 (1.6) | 0 (0) | 0.999 |
| | | 20–70 × $10^9$/l, n (%) | 2 (1.1) | 2 (6.9) | 0.088 |
| | Leucocyte count ($10^9$/l) | | 13.1 [9.9–17.2] | 11.0 [6.4–14.0] | **0.011** |
| | % lymphocytes | | 50 [37–69] | 59 [51–70] | 0.238 |
| | % atypical lymphocytes | | 25 [10–47] | 18 [5–93] | 0.678 |
| | C-reactive protein (mg/l) | | 49 [42–67] | 18 [5–93] | 0.254 |
| | Transaminitis, n (%) | | 38 (20) | 17 (59) | **0.001** |
| | Lactate dehydrogenase ≥2 upper limit of normal, n (%) | | 7** (41) | 12*** (67) | 0.181 |

* injury while playing contact sports (n = 9), minor fall on the left side (n = 4), major fall (n = 3), heavy lifting (n = 1)

** assessed in 17 cases

*** assessed in 18 cases

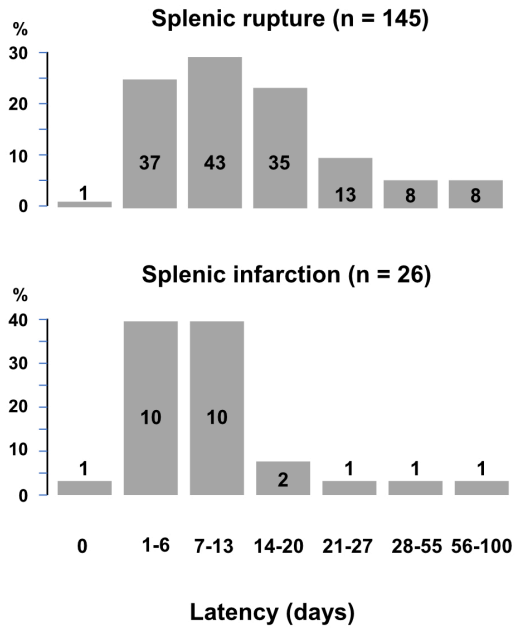
**Table 2:**
Relationship between World Society of Emergency Surgery splenic rupture score and management in patients with mononucleosis-associated splenic rupture.

| | World Society of Emergency Surgery splenic rupture score | | | | |
|---|---|---|---|---|---|
| | **All** | **Minor** | **Moderate** | **Severe** | **Unknown** |
| **n** | **186** | **53** | **68** | **55** | **10** |
| Operative, n (%)* | 108 (58) | 26 (49) | 35 (51) | 41 (75) | 6 (60) |
| Failure of non-operative management, n (%)* | 14 (7.5) | 1 (1.8) | 8 (12) | 5 (9.0) | 0 (0) |
| Non-operative, n (%) | 64 (34) | 26 (49) | 25 (37) | 9 (16) | 4 (40) |

* While 46 out of 55 cases with a severe rupture score were splenectomised, this figure (70 out of 121 cases) was lower (p = 0.001) for cases with a minor or moderate rupture score.

died [30, 43, 70, 83, 93, 101, 126, 129]: six had been admitted with signs of irreversible circulatory shock; the other three died after initial fluid resuscitation and urgent splenectomy. Fatal cases were temporally distributed as follows: 0 in 1970–1979, 2 in 1980–1989, 4 in 1990–1999, 1 in 2000–2009 and 2 in 2010–2022.

**Figure 2:** Time from onset of symptoms of Epstein-Barr virus infectious mononucleosis and onset of symptoms of splenic rupture or infarction.




### Splenic infarction

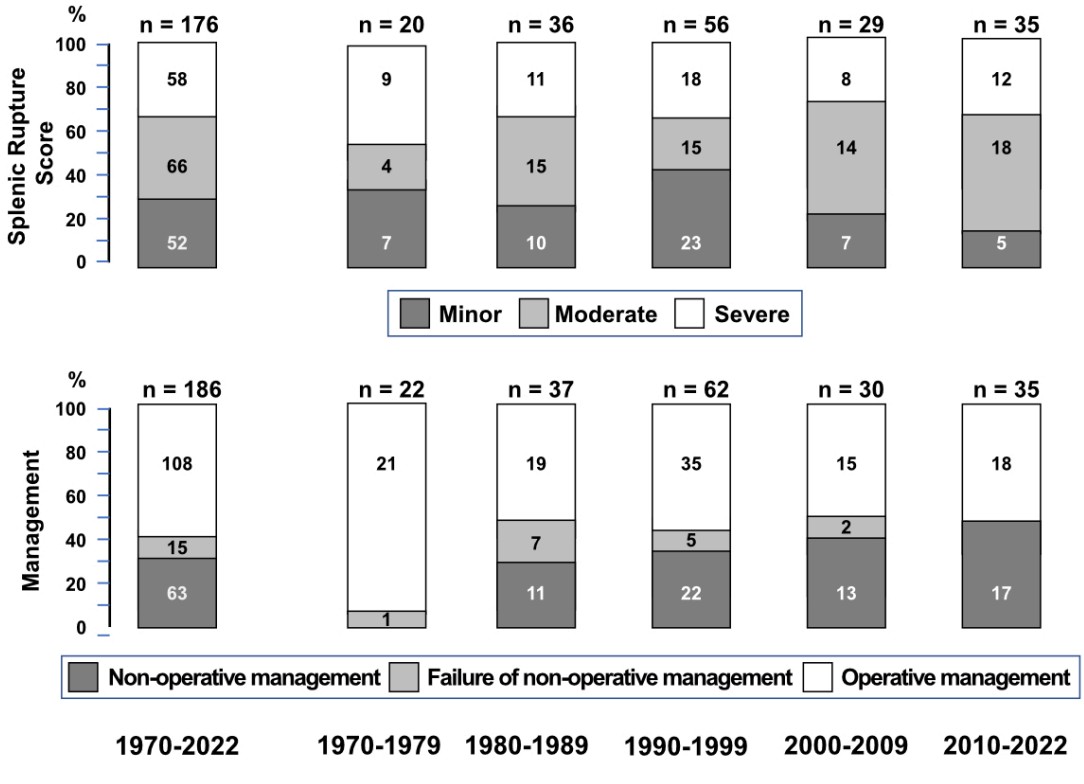
An underlying haematological disease was observed in 6 (21%) of the 29 patients with splenic infarction: hereditary spherocytosis in 4 and sickle cell trait in 2. One patient had coeliac disease. Furthermore, one patient concomitantly had Crohn's disease, sacroiliitis and Hashimoto's thyroiditis. Finally, one female subject was taking hormonal contraception. Interestingly, a transient elevation of the antiphospholipid level was noted in one patient.

The management was non-operative in all 29 patients. A splenectomy was performed one month or more after diagnosis in two patients with spherocytosis and in one patient with long-lasting abdominal pain and fatigue. None of the 29 patients died.

## Discussion

This systematic review of the literature focuses on two complications of mononucleosis [1–3]: splenic rupture and splenic infarction. The results may be summarised as follows. Both rupture and infarction predominantly occur in males, usually 15 to 30 years of age, and present one to three weeks after the onset of mononucleosis symptoms (which are mild in about 20% of cases) with acute abdominal pain, which is mostly diffuse (but often predominates in the left upper quadrant), and left shoulder pain. Haemodynamic instability secondary to a circulatory shock occurs in approximately one-third of cases of splenic rupture, which is still potentially fatal. Moreover, cases with infarction quite frequently have a pre-existing haematological condition such as spherocytosis or sickle cell trait. Finally, and especially clinically relevant, a spleen-preserving

**Figure 3:** World Society of Emergency Surgery splenic rupture score in patients with splenic rupture associated with Epstein-Barr virus infectious mononucleosis.



treatment is nowadays a viable alternative to splenectomy in mononucleosis-associated splenic rupture.

The cases included in this review were categorised as minor, moderate or severe on the basis of the three-point scoring system recommended by the World Society of Emergency Surgery (WSES) for patients with splenic trauma [12]. In the patients with Epstein-Barr virus-associated splenic rupture included in this analysis, this scoring system, which is simpler than the five-point spleen injury scale endorsed by the American Association for the Surgery of Trauma and includes both clinical and imaging data [185], correlates well with required management.

Given the rarity of mononucleosis-associated splenic rupture, there is no clear consensus on treatmentstrategy. Non-operative management of haemodynamically stable cases, i.e. with a minor or moderate WSES rupture score, is currently the standard of care. In addition to an expectant attitude, non-operative management currently includes splenic artery embolisation [6–8, 117, 186]. Partial splenectomy and splenic repair are no longer recommended [187]. The recommended treatment must be approached with caution given the risk of ongoing bleeding and the potential for late rupture. These patients should be cared for by an experienced multidisciplinary team, with physical activity restriction after discharge. Specifically, no activity more vigorous than walking is recommended until splenomegaly has resolved on clinical examination, followed by a period of no contact sports for six months or until the splenic architecture normalises on imaging evaluation. In view of radiation concerns with CT scans, ultrasound should be the main imaging modality in children, adolescents and women of childbearing age [188].

In splenectomised patients, prevention of infections is crucial. Recommended methods to decrease the infection risk include patient education, vaccination and antimicrobial prophylaxis [7, 9]. Although this review challenges the long-standing belief [4, 28] that palpation may induce mononucleosis-associated splenic rupture, it still seems judicious to avoid vigorous abdominal palpation in this setting.

Generally, splenic infarction is an uncommon diagnosis [5, 189]. Thromboembolism —either of cardiovascular origin or as the result of a thrombophilia— and a rapidly enlarging spleen —such as in the case of oncological or non-oncological haematological diseases and acute infections— are the main causes. The results of our review suggest that mononucleosis-associated splenic infarction is often not caused by the Epstein-Barr virus infection alone but also by a pre-existing haematological condition. A high index of suspicion for splenic infarction is appropriate in subjects with the mentioned predisposing conditions presenting with left upper abdominal pain, with or without associated left shoulder pain. The data of this review does not support the use of the lactatedehydrogenase test as a diagnostic tool in cases with suspected infarction. The most appropriate diagnostic imaging is CT with intravenous contrast [5]. Regrettably, Doppler ultrasound is of limited diagnostic value.

The main limitation of this systematic review relates to the rarity of these two complications. Hence, we collected information from cases published between 1970 and 2022, which were sometimes not thoroughly documented. Three well-accepted databases and Google Scholar were used for our literature search. It seems to us highly improbable that substantially different results would have been obtained if additional databases had been searched. Furthermore, the recommended treatment strategy does not arise from well-designed studies but is mainly extrapolated from current guidelines on the management of traumatic splenic rupture [6–8]. The main strength of the study relates to the relatively high number of included cases. Furthermore, this is the first report which investigates the literature on mononucleosis-associated splenic infarction.

In conclusion, this systematic review of the literature documents that, like with traumatic splenic rupture, splenic preservation is increasingly common in the management of mononucleosis-associated splenic rupture, with mainly good success. The treatment strategy is dictated by haemodynamic parameters. Sadly, even in the third millennium, this disease is still occasionally fatal.

## Data availability statement

The data supporting the current analysis can be found on the data repository Zenodo (https://zenodo.org/record/7711236).

### Authorship contribution statement

JMAT, BG, MGB, GPM, SAGL and PC designed and contributed to the systematic review; JMAT and BG performed the literature search, the selection of cases, the data extraction and the evaluation of comprehensiveness; JMAT entered the data into a worksheet, BG verified the accuracy of data entry; JMAT and BG performed the data analysis; GPM supervised the literature search, the selection of cases, the data extraction, the evaluation of comprehensiveness, data entry, accuracy of data entry and data analysis; JMAT, BG, IH, MGB and SAGL drafted the article, all other authors critically reviewed the article before submission.

### Funding

SAGL is the current recipient of research grants from Fonds de perfectionnement, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Fondation SICPA, Prilly, Switzerland; Fondazione Dr. Ettore Balli, Bellinzona, Switzerland; Fondazione per il bambino malato della Svizzera italiana, Bellinzona, Switzerland; and Frieda Locher-Hofmann Stiftung, Zürich, Switzerland.

### Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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