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REVIEW ARTICLE

Prevalence of Compartment Syndrome and Disseminated Intravascular Coagulation following Rhabdomyolysis; a Systematic Review and Meta-Analysis

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Abstract: **Introduction:** Rhabdomyolysis (RM) may cause some complications such as compartment syndrome and disseminated intravascular coagulation (DIC), which can affect its prognosis. This systematic review and meta-analysis aimed to investigate the prevalence of the mentioned complications following RM. **Methods:** Medline, Embase, and Scopus databases were searched using keywords related to compartment syndrome, DIC, and rhabdomyolysis with appropriate combination. Cohort and cross-sectional studies that conducted research on the prevalence of compartment syndrome and DIC in patients with RM were included in the present study. The desired data were extracted from the included studies and meta-analysis was conducted on them to calculate pooled prevalence of these complications. **Results:** Twenty articles were included in our systematic review. The rate of compartment syndrome reported in these studies ranged from 0 to 30.7%. Our meta-analysis revealed the pooled prevalence of 4% (95% confidence interval (CI): 2.20 to 7.40) for compartment syndrome in these studies. The pooled prevalence of this complication was 7.1% (95% CI: 2.90 to 16.00) among patients with severe RM and 4.4% (95% CI: 1.80 to 10.00) in traumatic RM. The rate of DIC reported in the included studies ranged from 0 to 40.47%. Our meta-analysis showed the pooled prevalence of 8.3% (95% CI: 03.90 to 16.50) for this complication among RM patients. **Conclusion:** We reported the rates of compartment syndrome and DIC in RM patients based on rhabdomyolysis etiologies through an epidemiologic systematic review and meta-analysis. The rate of compartment syndrome was slightly higher in patients with severe RM and its rate in patients with traumatic RM was close to the overall rate of compartment syndrome.

Keywords: Rhabdomyolysis; Compartment syndromes; Disseminated intravascular coagulation; Systematic review

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1. Introduction

Rhabdomyolysis (RM) is a clinical condition characterized by a loss of muscle strength, muscle pain, and swelling. This condition is associated with a creatine kinase (CK) level exceeding 1000 IU/L or CK being more than five times the upper limit of normal (ULN) for a mild form of RM as per standard definition. If myoglobinuria and acute kidney injury (AKI) are present, it indicates a severe form of RM (1). The development of rhabdomyolysis is caused by an elevation of ionized calcium levels within the cytoplasm, which contributes to its pathogenesis. In theory, rhabdomyolysis

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can be triggered by various forms of muscle damage and any factors that result in or contribute to muscle damage (2). Among adults, the existing data indicate that the most frequent causes of rhabdomyolysis are drug or alcohol abuse, use of certain medications, traumatic injuries, neuroleptic malignant syndrome (NMS), and prolonged periods of immobility (3).

RM may cause some complications, which can affect its prognosis (4). The most important one is AKI, for which research indicated a wide range prevalence of 15% to over 50% in RM patients (3, 5, 6). However, besides AKI there are other complications that need to be noticed by clinicians; including compartment syndrome, disseminated intravascular coagulation (DIC), and electrolyte imbalance (7).

The release of muscle cells' content can cause local edema, which remains trapped within fascia and can lead to compartment syndrome (8). Compartment syndrome occurs when elevated pressure within a closed anatomical space poses a threat to the viability of muscles and nerves in that compartment. This condition arises due to compromised blood flow and localized ischemia (9). Although, there has not been sufficient evidence regarding its incidence rate in RM, it's not considered to be a rare complication (4). Hence, it is crucial to closely monitor clinical signs and compartment pressures with respect to compartment syndrome, as it has the potential to progress into a surgical emergency.

Disseminated intravascular coagulation is drastic activation of the coagulation system, leading to microvascular thrombosis and potentially life-threatening hemorrhage due to consumption of coagulation factors and platelets (10). The release of thromboplastin and other substances with prothrombotic properties from the injured muscle tissue in RM, especially severe forms of it, can cause DIC (4).

Due to the fact that DIC mostly occurs as a complication of severe medical conditions, its prevalence remains higher in more severe settings (11).

In this article our primary goal is to conduct an epidemiologic systematic review on published literature to report the prevalence of compartment syndrome and DIC in patients with RM based on the RM's etiology. Our secondary goal is to conduct a meta-analysis, if adequate data is available, to determine the pooled prevalence of these complications following RM.

2. Methods

2.1. Study design and setting

The present study is a systematic review of observational studies conducted with the aim of investigating the prevalence of compartment syndrome and DIC in patients with RM. Since this systematic review is dedicated to just reporting the prevalence of an event in observational studies there is no comparison of data in this research. This systematic review conforms to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement (12). This study follows the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies in Epidemiology (MOOSE) (13).

2.2. Search strategy

To find an answer to the question of the present study, Medline, Embase, and Scopus databases were searched. Keywords related to compartment syndrome, DIC, and rhabdomyolysis were selected and then searched in each database with the appropriate combination. The keywords of search strategy for this study are reported in supplementary table 1. The search was conducted on April 30, 2023 and included every record till then. In addition to the systematic search, a manual search was also performed in gray literature. The search strategy is presented in the appendix.

2.3. Selection criteria

Two reviewers, I.N. and M.F.R independently screened the records by title/abstract and full text to exclude records unrelated to the topic. A third reviewer, B.D., would decide if the two reviews couldn't agree on a particular article. Cohort studies and cross-sectional studies in English, which conducted research on the prevalence of compartment syndrome and DIC in patients with RM were included in the present study. Exclusion criteria were failure to report compartment syndrome or DIC as an outcome, not identifying RM's etiologies, clinical trials, case-control studies, case reports, review studies, repeated studies, retracted studies, conference abstracts, editorials, and letters to editors.

2.4. Quality assessment

Assessment of the quality of included articles was done by two reviewers, B.D. and M.F.R., using the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools for observational cohort and cross-sectional studies (14). This tool is a 14-question checklist, based on which the quality of articles is assessed in terms of methodology, report of findings, and possible distortions. A third reviewer, A.S., would decide if the two reviews couldn't agree on a particular assessment.

2.5. Data extraction

Compartment syndrome and DIC prevalence were extracted from included articles, along with the etiology of rhabdomyolysis, age group of patients, and studies' demographic information such as data collection period, country, study design, and sampling method. We also collected data on definitions of these conditions in the included articles, when available. Collected data were summarized using a checklist designed

based on the MOOSE statement guidelines (13).

2.6. Statistical analysis

The prevalence of compartment syndrome and DIC in RM patients was investigated using the Comprehensive Meta-Analysis software, version 2.0 (Biostat Inc., Englewood, NJ, USA). we reported pooled prevalence with a 95% confidence interval (CI). Random effect model was used for groups of studies with significant heterogeneity between their research methodologies; and for groups of studies without significant heterogeneity, fixed effect model was used. In addition, if possible, subgroup analysis was performed based on the etiology and severity of RM. Finally, funnel plot and Egger's test were used to identify publication bias.

3. Results

At the last stage of our screenings there were 20 articles, which were included in our systematic review via selection process (figure 1). Six of them were conducted in USA (15-20), two in Australia (21, 22), two in Norway (23, 24), and 10 in other countries, which can be seen in table 1. All studies were retrospective cohorts except one, which was cross-sectional (25). The sampling method in all of the included studies were consecutive. 17 studies consisted only of adult patients (18 years old or above) and the three remaining studies consisted of children as well as adults. The total number of RM patients in these studies were 1310 patients, approximately 55% of which were male.

Quality of included articles was assessed based on NHLBI quality assessment tool (supplementary table 2). Included articles were rated as poor quality (0 to 4 out of 14 questions), fair quality (5 to 10 out of 14 questions), or good quality (11 to 14 out of 14 questions). All included studies had fair quality.

3.1. Compartment syndrome prevalence in included studies

Sixteen of the included studies reported compartment syndrome prevalence in RM patients. There were 928 adults with RM in these studies, approximately 54% of which were male. RM definitions were different in these studies. One study defined RM patients as having International Classification of Diseases (ICD) version 9 code related to RM diagnosis (17). Other studies defined RM disease by the level of the creatine kinase (CK) enzyme in blood of the patients. Most authors diagnosed rhabdomyolysis based on CK levels five times the upper limit of normal levels (>1000 U/L) (16, 19, 20, 22, 23, 25-28). This diagnostic cut-off was lower than 1000 in one study (15), and four studies exclusively included patients with CK levels more than 5000 (15, 21, 24, 29, 30). CK level more than 5000 is considered to indicate severe RM (31). The criteria for RM definition were not available in one study (32).

The primary etiologies in these patients comprise exercise, earthquake-related trauma, snake venom, drug toxicity, prolonged immobilization, and surgery (table 2). The compartment syndrome definition was not reported in most of the included articles. One study mentioned clinical diagnosis by a surgeon (24) and another one mentioned requirement of fasciotomy (22) as compartment syndrome diagnosis method.

The rate of compartment syndrome in the included studies ranged from 0% to 30.7%. The pooled prevalence of compartment syndrome was 4% (95% CI: 2.20 to 7.40; $p < 0.001$) in these studies (figure 2). Due to the high levels of heterogeneity between these studies we tried to conduct a sub-group analysis based on RM severity, and RM etiology dividing RM causes between traumatic and non-traumatic etiologies. Traumatic causes included exercise, earthquake trauma, prolonged immobilization, and surgery. The pooled prevalence of compartment syndrome in severe RM cases was 7.1% (95% CI: 2.90 to 16.00; $p < 0.001$; supplementary figure 1). The pooled prevalence of this complication in trauma-induced RM was 4.4% (95% CI: 1.80 to 10.00, $p < 0.001$; supplementary figure 2). Finally, the publication bias was investigated via funnel plot and Egger's test, which showed no significant publication bias (supplementary figure 3).

3.2. DIC prevalence in included studies

Ten of the included studies reported the prevalence of DIC syndrome or related hematologic failures in RM patients. There were 797 patients with RM in these studies, approximately 53% of which were male. RM definitions were different in these studies. The RM definition in one study was based on International Classification of Diseases (ICD) version 9 code related to RM diagnosis (18). Like in articles related to compartment syndrome, most studies diagnosed rhabdomyolysis based on CK levels five times the upper limit of normal levels (>1000 U/L) (19, 26, 27, 33-35). Two studies exclusively included patients with CK levels more than 5000 (24, 29). Criteria for RM diagnosis were not available in one study (32).

The primary etiologies in these patients comprised exercise, salicylate intoxication, snake venom, drug toxicity, mushroom poisoning, and exertional heat stroke, as shown in table 3. The DIC syndrome definition was not reported in most of the included articles. Korean Society on Thrombosis and Hemostasis (KSTH) DIC scoring system and International Society for Thrombosis and Hemostasis (ISTH) DIC scoring system were used as criteria for DIC syndrome diagnosis in two of the studies (26, 35). One study only mentioned hematologic failure as outcome of RM (18).

DIC syndrome prevalence in RM patients in the included studies ranged from 0% to 40.47%. Our meta-analysis showed the pooled prevalence of 8.3% (95% CI: 03.90 to 16.50; $p < 0.001$) in all studies (figure 3). Due to the high levels

of heterogeneity between these studies, we tried to conduct a sub-group analysis based on RM severity and etiology. However, because of the insufficient number of studies in these sub-groups it was not possible. Publication bias was investigated using funnel plot and Egger's test, which revealed no significant publication bias in the included studies (supplementary figure 4).

4. Discussion

Compartment syndrome and disseminated intravascular coagulation are two of the serious complications that can arise following rhabdomyolysis (36-38). If these complications occur, they can significantly impact the prognosis of the disease and result in morbidity and mortality for RM patients (39). Compartment syndrome is not a rare finding in rhabdomyolysis (4). It can induce ischemia in the affected area, impeding the healing process and exacerbating RM in a self-perpetuating vicious loop (40, 41). DIC can trigger systemic hematologic and circulatory dysfunction, giving rise to life-threatening events such as severe hemorrhage and organ failure (42).

Therefore, it is important to investigate the occurrence rate of these complications among individuals with rhabdomyolysis.

The overall prevalence of compartment syndrome in our study was calculated to be 4% (95% CI: 2.20 to 7.40). It has been shown that the majority of cases of acute compartment syndrome occur after trauma, with an estimated incidence of 7.3 per 100,000 in males and 0.7 per 100,000 in females (9). As we showed in this systematic review, it can result from rhabdomyolysis with both traumatic and non-traumatic origins. However, the rate of compartment syndrome was much higher in the study that included patients with RM due to the earthquake trauma (25). The pooled prevalence of this complication in exclusive trauma-induced RM was 4.4% (95% CI: 1.80 to 10.00) in our study, which is close to overall prevalence. The pooled prevalence of compartment syndrome calculated from studies exclusively reporting severe RM was 7.1% (95% CI: 2.90 to 16.00) and the etiology of RM in all of them was exercise. We classified severe rhabdomyolysis as having creatine kinase (CK) levels exceeding 5000 IU/L. Other studies also have reported that CK levels higher than 4000 IU/L are associated with compartment syndrome (43, 44).

In the present study, pooled prevalence of DIC syndrome was calculated to be 8.3% (95% CI: 03.90 to 16.50). Direct comparison and analysis of the incidence of DIC across studies is challenging due to various factors. For instance, diagnostic scoring systems for DIC are not consistently utilized in all hospitals, and different criteria have been employed to diagnose it (10). The studies in this field may underestimate the actual prevalence of DIC, especially mild, subclinical, and transient episodes, since they might have no clinical manifestations (4). In one study conducted in Japan the rate of DIC was reported to be 1% in hospitalized patients (45). This rate was reported to be approximately 10 to 30% in intensive care unit (ICU) patients (46-50). Studies also suggested approximate rate of 8 to 33% in patients resuscitated from out-of-hospital cardiac arrest (51, 52) and 36 to 41% in patients with head trauma (53, 54).

Our study holds some limitations. The small population size in the included studies and the limited number of these studies were limitations that needed to be noticed. Many articles on DIC and compartment syndrome prevalence pertained to single-center studies, lacked specific definitions of these complications, were published long ago, and did not provide evidence on presence of confounding factors and comorbidities that can play a role in occurrence of these complications. These limitations highlight the need of new researches on the epidemiology of DIC and compartment syndrome in rhabdomyolysis patients with larger population and utilizing standard diagnostic criteria to report their incidence.

Furthermore, conduction of meta-analysis on observational studies is challenging due to the inherent limitations of the observational studies. Observational studies cannot address all potential confounding factors and the heterogeneity among these studies is usually high. Despite efforts to maintain methodological consistency and control for confounding factors, such as sub-group analysis and using random effects model, complete homogeneity cannot be achieved (55). Further studies are needed to investigate prevalence and tolls of these complications in larger populations of RM patients.

5. Conclusion

According to our results the pooled prevalence of compartment syndrome and DIC in RM patients were 4% (95% CI: 2.20 to 7.40) and 8.3% (95% CI: 03.90 to 16.50) respectively. The rate of compartment syndrome was slightly higher in patients with severe RM and its rate in patients with traumatic RM was close to the overall rate of compartment syndrome in all RM patients.

6. Declarations

6.1. Acknowledgments

Not applicable.

6.2. Conflict of interest

The authors declare no competing interests.

6.3. Funding and support

None.

6.4. Authors' contribution

All the authors met the criteria of authorship based on the recommendations of the international committee of medical journal editors and read and accepted the final manuscript.

6.5. Data Availability

All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

References

1. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. J Neurol. 2020;267(4):877-82.
2. Torres PA, Helmstetter JA, Kaye AM, Kaye AD. Rhabdomyolysis: pathogenesis, diagnosis, and treatment. Ochsner J. 2015;15(1):58-69.
3. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore). 2005;84(6):377-85.
4. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore). 2005;84(6):377-85.
5. Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. Medicine (Baltimore). 1982;61(3):141-52.
6. Veenstra J, Smit WM, Krediet RT, Arisz L. Relationship between elevated creatine phosphokinase and the clinical spectrum of rhabdomyolysis. Nephrol Dial Transplant. 1994;9(6):637-41.
7. Stanley M, Chippa V, Aeddula NR, Quintanilla Rodriguez BS, Adigun R. Rhabdomyolysis. StatPearls. Treasure Island (FL): StatPearls Publishing. Copyright © 2023, StatPearls Publishing LLC.; 2023.
8. Grau JM, Poch E. Pathophysiology and management of rhabdomyolysis. In: Webb A, Angus D, Finfer S, Gattinoni L, Singer M, editors. Oxford Textbook of Critical Care: Oxford University Press; 2016. p. 0.
9. Torlincasi AM, Lopez RA, Waseem M. Acute Compartment Syndrome. StatPearls. Treasure Island (FL): StatPearls Publishing. Copyright © 2023, StatPearls Publishing LLC.; 2023.
10. Adelborg K, Larsen JB, Hvas AM. Disseminated intravascular coagulation: epidemiology, biomarkers, and management. Br J Haematol. 2021;192(5):803-18.
11. Costello RA, Nehring SM. Disseminated Intravascular Coagulation. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
13. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama. 2000;283(15):2008-12.
14. Health NIo. Study quality assessment tools. 2014 2021 [Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
15. Arnautovic JZ, Tereziu S. Evaluation of Clinical Outcomes in Hospitalized Patients With Exertional Rhabdomyolysis. J Am Osteopath Assoc. 2019;119(7):428-34.
16. Backer HC, Busko M, Krause FG, Exadaktylos AK, Klukowska-Roetzler J, Deml MC. Exertional rhabdomyolysis and causes of elevation of creatine kinase. Phys Sportsmed. 2020;48(2):179-85.
17. Van Eck NJ, Waltman L. Text mining and visualization using VOSviewer. arXiv preprint arXiv:11092058. 2011:1-5.
18. Kaewput W, Thongprayoon C, Petnak T, Cheungpasitporn W, Qureshi F, Boonpheng B, et al. Rhabdomyolysis among hospitalized patients for salicylate intoxication in the United States: Nationwide inpatient sample 2003-2014. PLOS ONE. 2021;16(3):e0248242.
19. Luetmer MT, Boettcher BJ, Franco JM, Reisner JH, Cheville AL, Finnoff JT. Exertional Rhabdomyolysis: A Retrospective Population-based Study. Med Sci Sports Exerc. 2020;52(3):608-15.
20. O'Connor AD, Padilla-Jones A, Gerkin RD, Levine M. Prevalence of Rhabdomyolysis in Sympathomimetic Toxicity: a Comparison of Stimulants. J Med Toxicol. 2015;11(2):195-200.
21. Huynh A, Leong K, Jones N, Crump N, Russell D, Anderson M, et al. Outcomes of exertional rhabdomyolysis following high-intensity resistance training. Intern Med J. 2016;46(5):602-8.
22. Lau Hing Yim C, Wong EWW, Jellie LJ, Lim AKH. Illicit drug use and acute kidney injury in patients admitted to hospital with rhabdomyolysis. Intern Med J. 2019;49(10):1285-92.
23. Vangstad M, Bjornaas MA, Jacobsen D. Rhabdomyolysis: a 10-year retrospective study of patients treated in a medical department. Eur J Emerg Med. 2019;26(3):199-204.
24. Tazmini K, Schreiner C, Bruserud S, Raastad T, Solberg EE. Exercise-induced rhabdomyolysis - a patient series. Tidsskr Nor Laegeforen. 2017;137(21).
25. Li CY, Lin CH, Chang CW, Chuang CH, Chung YH, Hu MH, et al. Musculoskeletal injuries and management of victims from collapsed buildings in the 2016 Taiwan earthquake: Experiences in a tertiary medical center. Injury. 2021;52(11):3334-9.

26. Moon JM, Chun BJ, Cho YS. Clinical features of snake envenomation in South Korea. Clin Toxicol (Phila). 2023;61(4):276-82.
27. Rogliano PF, Voicu S, Labat L, Deye N, Malissin I, Laplanche JL, et al. Acute Poisoning with Rhabdomyolysis in the Intensive Care Unit: Risk Factors for Acute Kidney Injury and Renal Replacement Therapy Requirement. Toxics. 2020;8(4).
28. Youssef T, Abd-Elaal I, Zakaria G, Hasheesh M. Bariatric surgery: Rhabdomyolysis after open Roux-en-Y gastric bypass: a prospective study. Int J Surg. 2010;8(6):484-8.
29. Jabur WL, Nasa P, Mohammed KA, Kulkarni A, Tomaraei SN. An Observational Epidemiological Study of Exercise-induced Rhabdomyolysis Causing Acute Kidney Injury: A Single-center Experience. Indian J Nephrol. 2018;28(2):101-4.
30. Shroff K, Gunasegaren M, Norbu K, Omar E. Clinical characteristics of spinning-induced rhabdomyolysis and other causes of rhabdomyolysis: a comparative study. Singapore Med J. 2022;63(10):567-71.
31. Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit Care. 2016;20(1):135.
32. Hernandez-Contreras ME, Torres-Roca M, Hernandez-Contreras V, Rosa Salazar V, Mar Garcia-Mendez M, Garcia-Perez B, et al. Rhabdomyolysis after initial session of indoor cycling: analysis of 11 patients. J Sports Med Phys Fitness. 2015;55(11):1371-5.
33. Nishimura H, Enokida H, Kawahira S, Kagara I, Hayami H, Nakagawa M. Acute Kidney Injury and Rhabdomyolysis After Protobothrops flavoviridis Bite: A Retrospective Survey of 86 Patients in a Tertiary Care Center. Am J Trop Med Hyg. 2016;94(2):474-9.
34. Trakulsrichai S, Jeeratheepatanont P, Sriapha C, Tongpoo A, Wananukul W. Myotoxic Mushroom Poisoning in Thailand: Clinical Characteristics and Outcomes. Int J Gen Med. 2020;13:1139-46.
35. Wang C, Yu B, Chen R, Su L, Wu M, Liu Z. Association of D-dimer and acute kidney injury associated with rhabdomyolysis in patients with exertional heatstroke: an over 10-year intensive care survey. Ren Fail. 2021;43(1):1561-8.
36. Bhalla MC, Dick-Perez R. Exercise induced rhabdomyolysis with compartment syndrome and renal failure. Case Rep Emerg Med. 2014;2014:735820.
37. Iftikhar MH, Dar AY, Haw A. Cocaine-induced rhabdomyolysis and compartment syndrome. BMJ Case Rep. 2022;15(5).
38. Yun DH, Suk EH, Ju W, Seo EH, Kang H. Fatal rhabdomyolysis and disseminated intravascular coagulation after total knee arthroplasty under spinal anesthesia: A case report. World J Clin Cases. 2022;10(4):1349-56.
39. Keltz E, Khan FY, Mann G. Rhabdomyolysis. The role of diagnostic and prognostic factors. Muscles Ligaments Tendons J. 2013;3(4):303-12.
40. Better OS, Rubinstein I, Reis DN. Muscle crush compartment syndrome: fulminant local edema with threatening systemic effects. Kidney Int. 2003;63(3):1155-7.
41. Slater MS, Mullins RJ. Rhabdomyolysis and myoglobinuric renal failure in trauma and surgical patients: a review. J Am Coll Surg. 1998;186(6):693-716.
42. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care. 2014;2(1):15.
43. Valdez C, Schroeder E, Amdur R, Pascual J, Sarani B. Serum creatine kinase levels are associated with extremity compartment syndrome. J Trauma Acute Care Surg. 2013;74(2):441-5; discussion 5-7.
44. Weingart GS, Jordan P, Yee KL, Green L. Utility of laboratory markers in evaluating for acute compartment syndrome in the emergency department. J Am Coll Emerg Physicians Open. 2021;2(1):e12334.
45. Matsuda T. Clinical aspects of DIC–disseminated intravascular coagulation. Pol J Pharmacol. 1996;48(1):73-5.
46. Angstwurm MW, Dempfle CE, Spannagl M. New disseminated intravascular coagulation score: A useful tool to predict mortality in comparison with Acute Physiology and Chronic Health Evaluation II and Logistic Organ Dysfunction scores. Crit Care Med. 2006;34(2):314-20; quiz 28.
47. Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med. 2004;32(12):2416-21.
48. Gando S, Saitoh D, Ogura H, Mayumi T, Koseki K, Ikeda T, et al. Natural history of disseminated intravascular coagulation diagnosed based on the newly established diagnostic criteria for critically ill patients: results of a multicenter, prospective survey. Crit Care Med. 2008;36(1):145-50.
49. Sivula M, Tallgren M, Pettila V. Modified score for disseminated intravascular coagulation in the critically ill. Intensive Care Med. 2005;31(9):1209-14.
50. Toh CH, Downey C. Performance and prognostic importance of a new clinical and laboratory scoring system for identifying non-overt disseminated intravascular coagulation. Blood Coagul Fibrinolysis. 2005;16(1):69-74.
51. Buchtele N, Schober A, Schoergenhofer C, Spiel AO, Mauracher L, Weiser C, et al. Added value of the DIC score and of D-dimer to predict outcome after successfully resuscitated out-of-hospital cardiac arrest. Eur J Intern Med. 2018;57:44-8.

52. Kim J, Kim K, Lee JH, Jo YH, Kim T, Rhee JE, et al. Prognostic implication of initial coagulopathy in out-of-hospital cardiac arrest. Resuscitation. 2013;84(1):48-53.
53. Sun Y, Wang J, Wu X, Xi C, Gai Y, Liu H, et al. Validating the incidence of coagulopathy and disseminated intravascular coagulation in patients with traumatic brain injury–analysis of 242 cases. Br J Neurosurg. 2011;25(3):363-8.
54. Hulka F, Mullins RJ, Frank EH. Blunt brain injury activates the coagulation process. Arch Surg. 1996;131(9):923-7; discussion 7-8.
55. Metelli S, Chaimani A. Challenges in meta-analyses with observational studies. Evid Based Ment Health. 2020;23(2):83-7.

Table 1: Characteristics of included articles

Authors	Publication year	Study period	Country	Study design	Age group	Sampling method
Arnautovic et al. (15)	2018	2014-2016	USA	R-Cohort	Adult	Consecutive
Bäcker et al. (16)	2019	2012-2017	USA	R-Cohort	Adult	Consecutive
Cutler et al. (17)	2015	2010-2014	USA	R-Cohort	Adult	Consecutive
Hernández-Contreras et al. (32)	2015	2012-2013	Spain	R-Cohort	Adult	Consecutive
Huynh et al. (21)	2016	2013-2014	Australia	R-Cohort	Adult	Consecutive
Jabur et al. (29)	2018	2009-2015	UAE	R-Cohort	Adult	Consecutive
Kaewput et al. (18)	2021	2003-2014	USA	R-Cohort	All ages	Consecutive
Li et al. (25)	2021	2016-2016	Taiwan	Cross-sectional	Adult	Consecutive
Luetmer et al. (19)	2020	2003-2015	USA	R-Cohort	Adult	Consecutive
Moon et al. (26)	2023	2010-2021	Korea	R-Cohort	Adult	Consecutive
Nishimura et al. (33)	2016	2003-2014	Japan	R-Cohort	Adult	Consecutive
O'Connor et al. (20)	2014	2010-2013	USA	R-Cohort	All ages	Consecutive
Rogliano et al. (27)	2020	2012-2018	France	R-Cohort	Adult	Consecutive
Shroff et al. (30)	2022	2018-2019	Singapore	R-Cohort	Adult	Consecutive
Tazmini et al. (24)	2017	2011-2015	Norway	R-Cohort	Adult	Consecutive
Trakulsrichai et al. (34)	2020	2012-2016	Thailand	R-Cohort	All ages	Consecutive
Vangstad et al. (23)	2017	2003-2012	Norway	R-Cohort	Adult	Consecutive
Wang et al. (35)	2021	2008-2019	China	R-Cohort	Adult	Consecutive
Yim et al. (22)	2019	2013-2017	Australia	R-Cohort	Adult	Consecutive
Youssef et al. (28)	2010	2007-2009	Egypt	R-Cohort	Adult	Consecutive

R-Cohort: Retrospective Cohort.

Table 2: Compartment syndrome prevalence in rhabdomyolysis patients

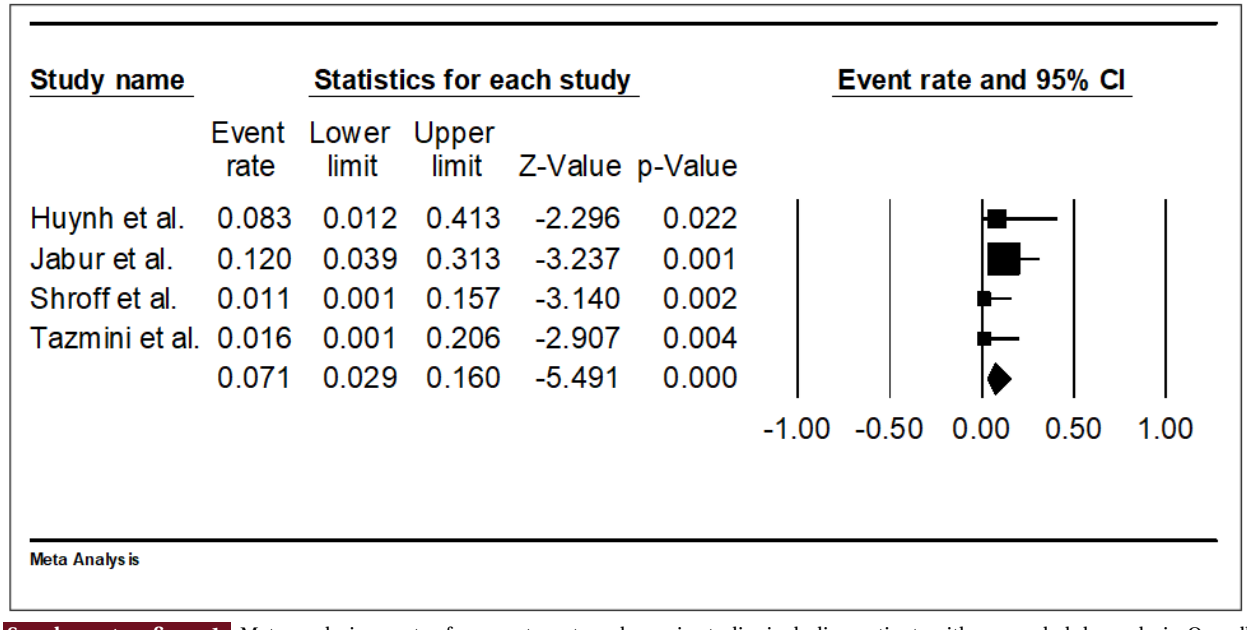
Authors	RM definition	Male n(%)	RM etiology	CS definition	CS prevalence n(%)
Arnautovic et al. (15)	CK > 342	41 (33)	Exercise	NR	0 (0)
Bäcker et al. (16)	CK ≥ 1000	42 (36)	Exercise	NR	0 (0)
Cutler et al. (17)	ICD-9 code 728.88	29 (18)	Exercise	NR	2 (6.89)
Hernández-Contreras et al. (32)	NR	11 (5)	Exercise	NR	0 (0)
Huynh et al. (21)	CK ≥ 25000	12 (11)	Exercise	NR	1 (8.33)
Jabur et al. (29)	CK > 5000	25 (25)	Exercise	NR	3 (12)
Li et al. (25)	CK more than 5 times the ULN value	13 (NR)	Earthquake trauma	NR	4 (30.76)
Luetmer et al. (19)	CK > 1000	21 (18)	Exercise	NR	0 (0)
Moon et al. (26)	CK ≥ 1000	90 (NR)	Snake venom	NR	1 (1.11)
O'Connor et al. (20)	CK > 1000	43 (NR)	Stimulant drugs toxicity	NR	3 (6.97)
Rogliano et al. (27)	CK ≥ 1000	237 (138)	Drug poisoning	NR	5 (2.11)
Shroff et al. (30)	CK > 20000	43 (21)	Exercise	NR	0 (0)
Tazmini et al. (24)	CK > 5000	31 (15)	Exercise	Clinical diagnosis by a surgeon	0 (0)
Vangstad et al. (23)	Male (18-49 years): CK > 2000 Male (age > 49 years): CK > 1400 Female: CK > 1050	204 (130)	Prolonged immobilization	NR	1 (0.49)
Yim et al. (22)	CK > 1000	79 (54)	Illicit drug use	Requirement of fasciotomy due to CS	3 (3.79)
Youssef et al. (28)	CK > 1000	7 (4)	Roux-en-Y gastric bypass bariatric surgery	NR	0 (0)

RM: Rhabdomyolysis; CK: Creatine Kinase; ULN: Upper Limit of Normal; CS: Compartment Syndrome; NR: Not Reported; ICD-9: International Classification of Diseases version 9.

Table 3: Disseminated intravascular coagulation (DIC) prevalence in rhabdomyolysis patients

Authors	RM definition	Male n(%)	RM etiology	DIC definition	DIC prevalence n(%)
Hernández-Contreras et al. (32)	NR	11 (5)	Exercise	NR	0 (0)
Jabur et al. (29)	CK > 5000	25 (25)	Exercise	NR	0 (0)
Kaewput et al. (18)	identified by the ICD-9 diagnosis 728.88	258 (136)	Salicylate intoxication	Hematological failure	30 (11.62)
Luetmer et al. (19)	CK > 1000	21 (18)	Exercise	NR	1 (4.76)
Moon et al. (26)	CK ≥ 1000	90 (NR)	Snake venom	KSTH DIC scoring system	1 (1.11)
Nishimura et al. (33)	CK more than 5 times the ULN value	7 (NR)	Snake venom	NR	1 (14.28)
Rogliano et al. (27)	CK ≥ 1000	237 (138)	Drug poisoning	NR	29 (12.23)
Tazmini et al. (24)	CK > 5000	31 (15)	Exercise	NR	0 (0)
Trakulsrichai et al. (34)	CK > 1000	33 (NR)	Mushroom poisoning	NR	1 (3.03)
Wang et al. (35)	CK > 1000	84 (84)	Exertional heatstroke	ISTH DIC scoring system	34 (40.47)

RM: Rhabdomyolysis; CK: Creatine Kinase; ULN: Upper Limit of Normal; NR: Not Reported; ICD-9: International Classification of Diseases version 9; KSTH: Korean Society on Thrombosis and Hemostasis; ISTH: International Society for Thrombosis and Hemostasis.



Supplementary figure 1: Meta-analysis on rate of compartment syndrome in studies including patients with severe rhabdomyolysis. Overall Heterogeneity: I^2 = 23.12%, P-value = 0.27. CI: confidence interval.

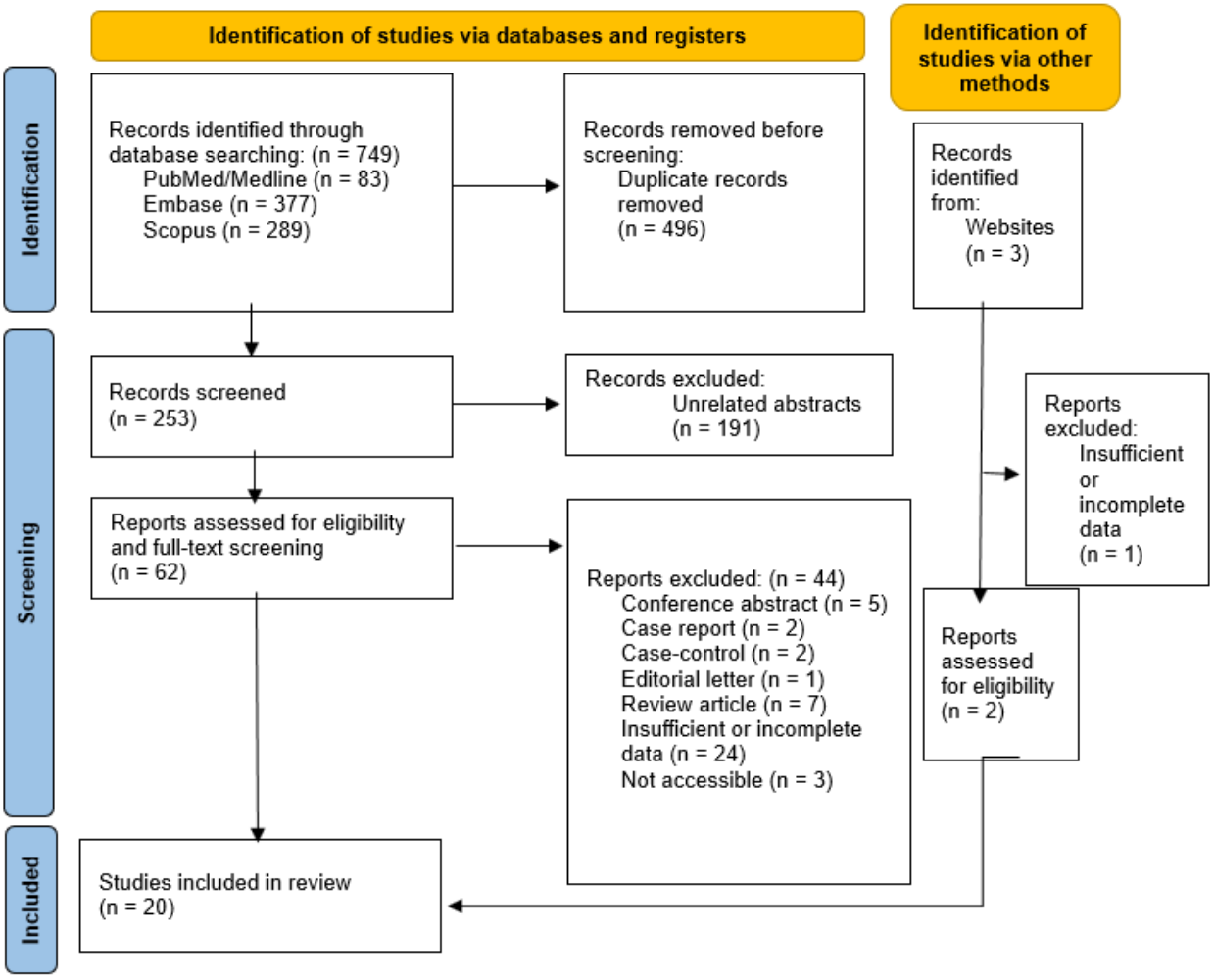


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the studies identified and included in the systematic review.

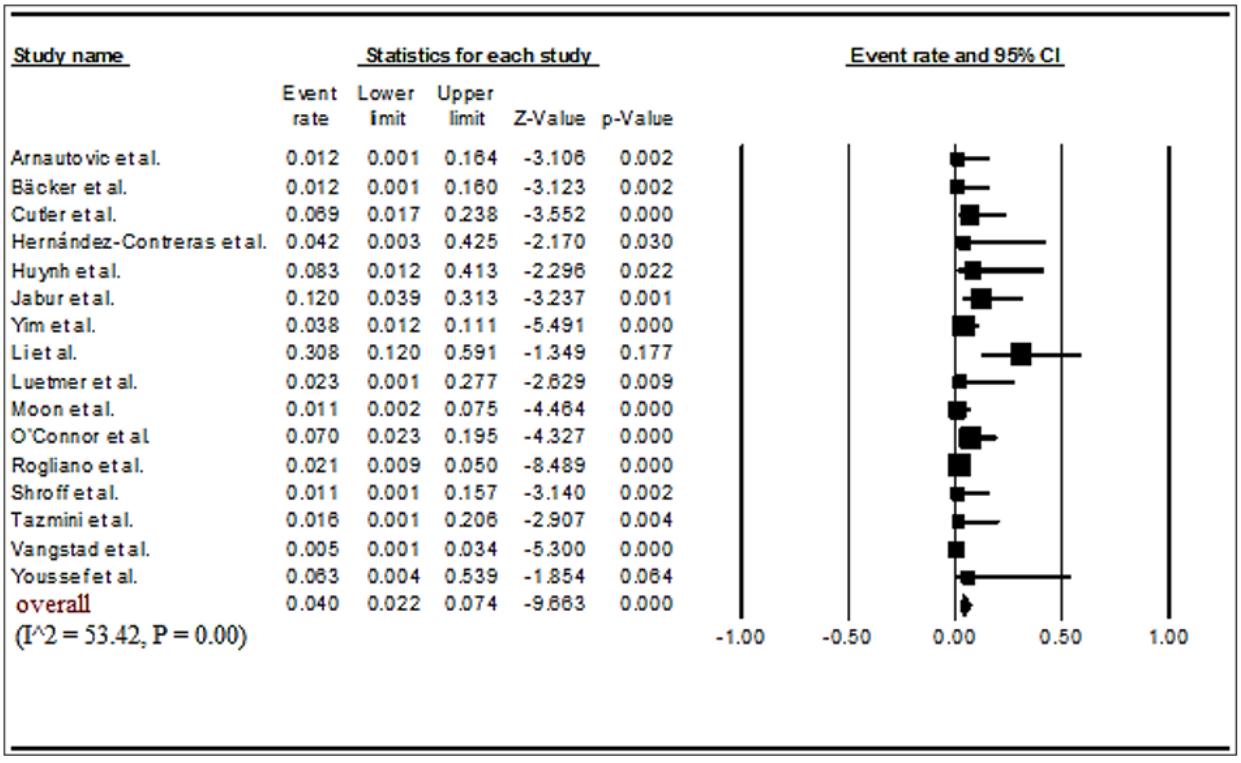


Figure 2: Results of meta-analysis of compartment syndrome prevalence in rhabdomyolysis patients. CI: confidence interval.

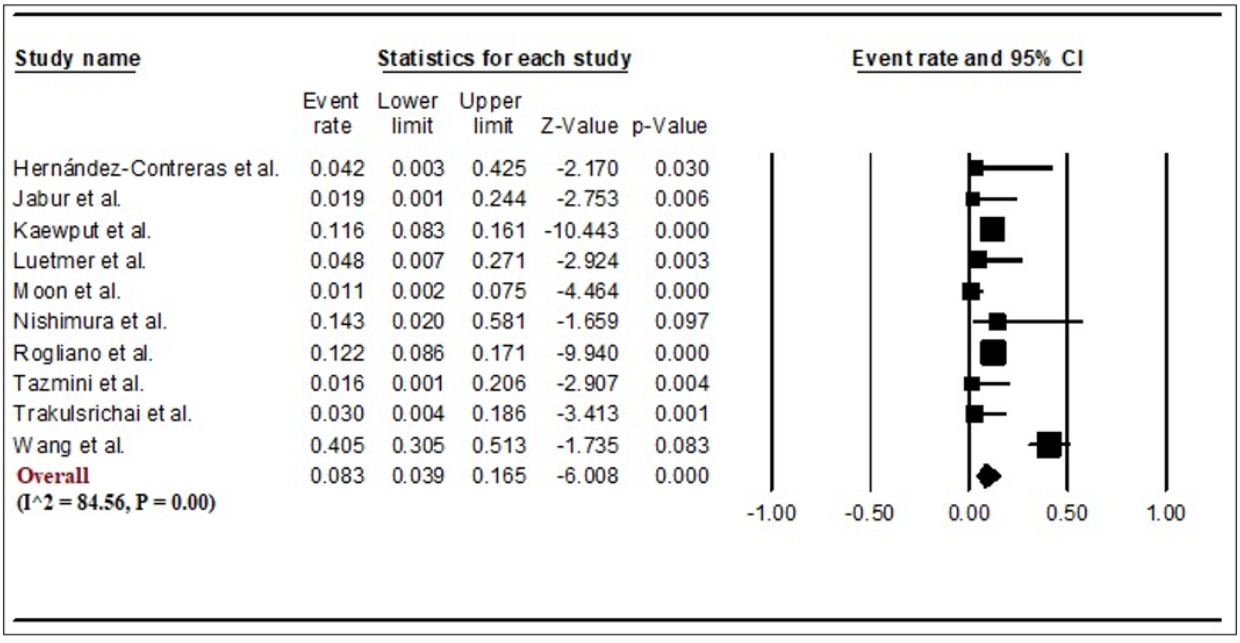
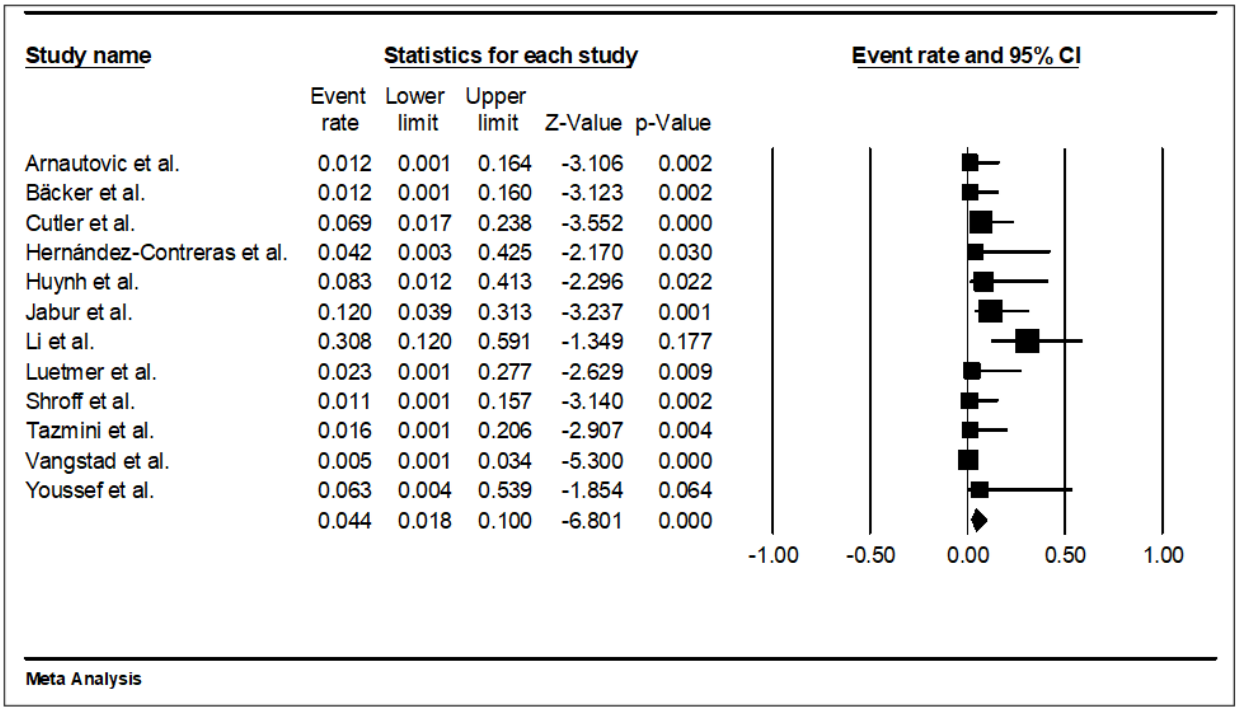
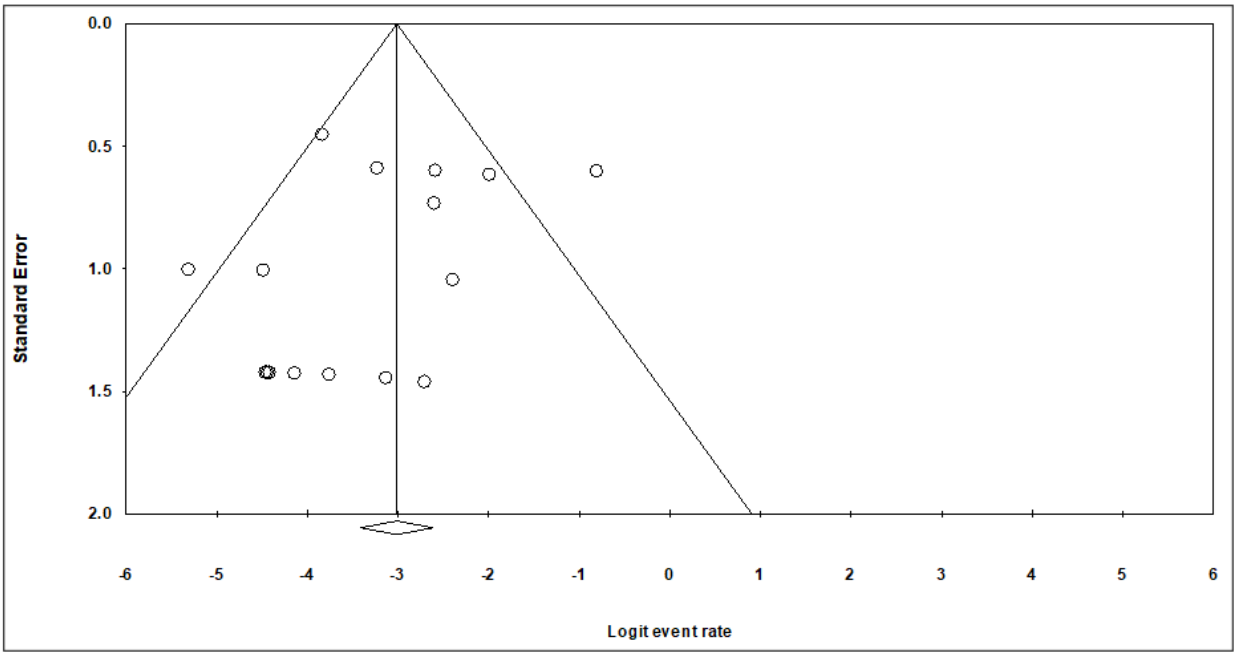


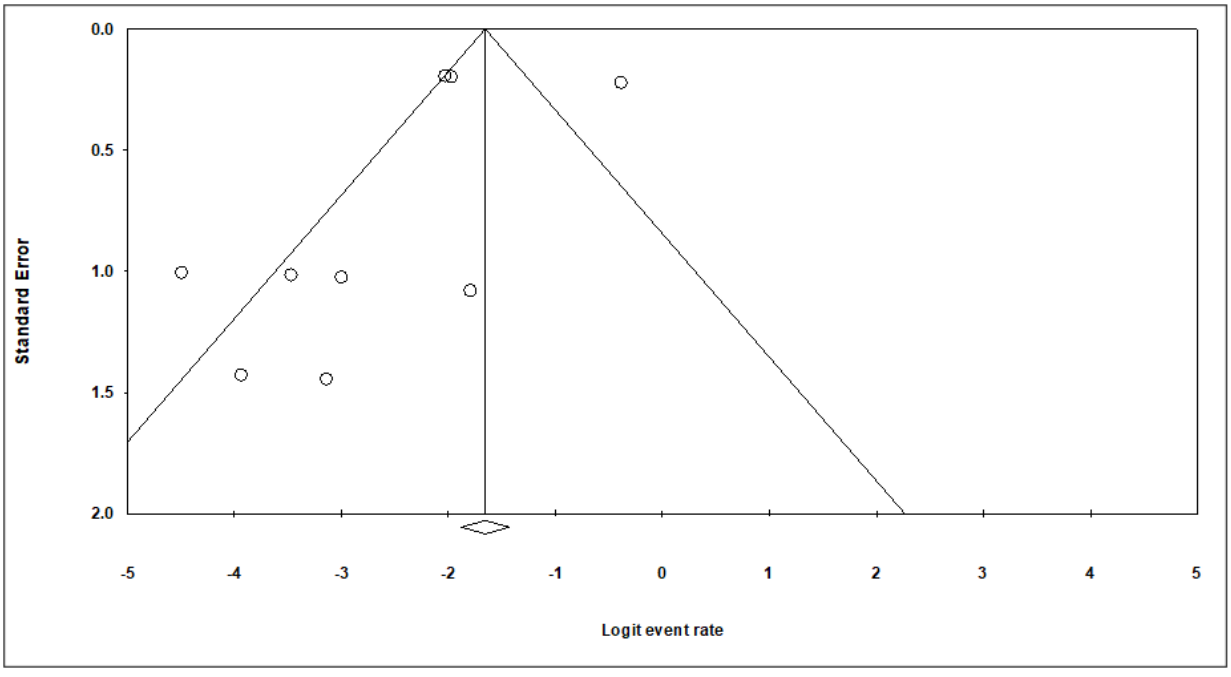
Figure 3: Results of meta-analysis of disseminated intravascular coagulation (DIC) syndrome prevalence in rhabdomyolysis patients. CI: confidence interval.



Supplementary figure 2: Meta-analysis on rate of compartment syndrome in studies including patients with traumatic rhabdomyolysis. Overall Heterogeneity: I^2 = 54.54%, P-value = 0.01. CI: confidence interval.



Supplementary figure 3: Publication bias assessment of included studies reporting compartment syndrome prevalence. Egger's regression test: Intercept = -1.18, Standard error = 0.90, P-value (2-tailed) = 0.21.



Supplementary figure 4: Publication bias assessment of included studies reporting disseminated intravascular coagulation (DIC) syndrome prevalence. Egger's regression test: Intercept = -1.69, Standard error = 1.28, P-value (2-tailed) = 0.23.