

Peer Review File

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Reviewer A

Comment 1: *The idea behind the paper is interesting, but already widely explored. Systematic reviews and meta-analyzes have existed on this topic for several years. There are similar paper, which examine the trend over time, as well as other markers, to create reliable scores on much larger samples of the paper in question.*

For this reason I find the paper interesting, but without an innovative message.

Response 1: Thank you for pointing this out. We agree with this comment. However, we would like to emphasize that we chose the same since the concept had not been extensively studied or utilized in hospitals in South India and we felt that this study would better help surgeons make decisions regarding management of polytrauma and multiple trauma patients.

Reviewer B

Comment 1:

Title: Very Good

Abstract: Very Good

Introduction and AIM: The problem and the aim are well describing.

Polytrauma patients are the very big challenge for emergency department. Please cite and discuss this paper:

Meccariello L, Razzano C, De Dominicis C, Herrera-Molpeceres JA, Liuzza F, Erasmo R, Rocca G, Bisaccia M, Pagliarulo E, Cirfeda P, Gómez Garrido D, Rollo G. A new prognostic pelvic injury outcome score. Med Glas (Zenica). 2021 Feb 1;18(1):299-308. doi: 10.17392/1298-21. PMID: 33307634.

Materials, Patients and methods and statistics: All good.

Results: Focus on and well described.

Discussion and Thread: effectiveness Focus ON.

The assessment of outcomes in the sport trauma pain, cite and discuss this paper:

Interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) levels in plasma and upper respiratory secretions directly correlate with the magnitude of viral replication, fever, and respiratory and systemic symptoms, including musculoskeletal clinical manifestations. The hit is like a polytrauma, discuss and cite this paper:

Ripani U, Bisaccia M, Meccariello L. Dexamethasone and Nutraceutical Therapy Can Reduce the Myalgia Due to COVID-19 - a Systemic Review of the Active Substances that Can Reduce the Expression of Interlukin-6. Med Arch. 2022 Feb;76(1):66-71. doi: 10.5455/medarh.2022.76.66-71. PMID: 35422571; PMCID: PMC8976893.

Trochanteric fractures are a major trauma in the elderly population and represent a significant part of public health spending. Various fixation devices are used as treatment for these fractures. This study aimed to evaluate three surgical methods in the treatment of pertrochanteric femoral fractures. Please cite and discuss this paper:

David GG, Michele B, Umberto R, Cioancă F, Andrea S, Alfonso C, Cristina IV, Maria ML, Antonio HJ, Giuseppe R, Luigi M. Metabolic Shock in Elderly Pertrochanteric or Intertrochanteric Surgery. Comparison of Three Surgical Methods. Is there a Much Safer? Rom J Anaesth Intensive Care. 2020 Dec;27(2):17-26. doi: 10.2478/rjaic-2020-0016. Epub 2020 Dec 31. PMID: 34056129; PMCID: PMC8158320.

ESR, CRP, and PCT proved to have a greater diagnostic accuracy in predicting late chronic and early postoperative infections, but to early sepsis shock? Please cite and discuss this paper:

Falzarano G, Piscopo A, Grubor P, Rollo G, Medici A, Pipola V, Bisaccia M, Caraffa A, Barron EM, Nobile F, Cioffi R, Meccariello L. Use of Common Inflammatory Markers in the Long-Term Screening of Total Hip Arthroprosthesis Infections: Our Experience. Adv Orthop. 2017;2017:9679470. doi: 10.1155/2017/9679470. Epub 2017 Aug 23. PMID: 29138696; PMCID: PMC5613705.

References: Well chosen but to improve

Figures and Table: Very Good.

Response 1: Thank you for pointing this out .We have, accordingly added certain points to the Introduction and Discussion to emphasize the point brought out by you.

1. Polytrauma patients are the very big challenge for emergency department. Please cite and discuss this paper:

Meccariello L, Razzano C, De Dominicis C, Herrera-Molpeceres JA, Liuzza F, Erasmo R, Rocca G, Bisaccia M, Pagliarulo E, Cirfeda P, Gómez Garrido D, Rollo G. A new prognostic pelvic injury outcome score. Med Glas (Zenica). 2021 Feb 1;18(1):299-308. doi: 10.17392/1298-21. PMID: 33307634.

Response: Manuscript Page 4, References (6)

According to Meccariello et al in his study,an ideal outcome score system should be simple, all inclusive, reliable and reproducible and should be able to provide prognostic information based on the outcomes of different fracture patterns to help a surgeon to improve preoperative planning and treatment to improve outcomes in patients with multiple injuries.(6)

The above mentioned is from the study recommended by you which we have gone through and included in the Introduction.

2.The hit is like a polytrauma, discuss and cite this paper:

Ripani U, Bisaccia M, Meccariello L. Dexamethasone and Nutraceutical Therapy Can Reduce the Myalgia Due to COVID-19 - a Systemic Review of the Active Substances that Can Reduce the Expression of Interlukin-6. Med Arch. 2022 Feb;76(1):66-71. doi: 10.5455/medarh.2022.76.66-71. PMID: 35422571; PMCID: PMC8976893.

Response: Page 7, Reference 11

Over recent years, therapeutic concepts of patients with major trauma have improved but organ dysfunction still remains a frequent complication since the concept of "Second hit" or "Third hit" of polytrauma is still not completely understood. (11)

This line has been added to the discussion. You have raised an important point here. However, we did not include the paper suggested because we have not included COVID 19 patients in our study since they are treated with corticosteroids and are hence excluded from our study based on our exclusion criteria.

3.Trochanteric fractures are a major trauma in the elderly population and represent a significant part of public health spending. Various fixation devices are used as treatment for these fractures. This study aimed to evaluate three surgical methods in the treatment of pertrochanteric femoral fractures. Please cite and discuss this paper:

David GG, Michele B, Umberto R, Cioancă F, Andrea S, Alfonso C, Cristina IV, Maria ML, Antonio HJ, Giuseppe R, Luigi M. Metabolic Shock in Elderly Pertrochanteric or Intertrochanteric Surgery. Comparison of Three Surgical Methods. Is there a Much Safer?

Rom J Anaesth Intensive Care. 2020 Dec;27(2):17-26. doi: 10.2478/rjaic-2020-0016. Epub 2020 Dec 31. PMID: 34056129; PMCID: PMC8158320.

Response: Thank you for this suggestion. It would have been interesting to explore this aspect. However, in the case of our study, it seems slightly out of scope because most of the study participants were mainly young and middle-aged with the mean age being 43.8 years who don't commonly sustain intertrochanteric and pertrochanteric fractures and hence we could not correlate our findings with those mentioned in this study.

4. ESR, CRP, and PCT proved to have a greater diagnostic accuracy in predicting late chronic and early postoperative infections, but to early sepsis shock? Please cite and discuss this paper:

Falzarano G, Piscopo A, Grubor P, Rollo G, Medici A, Pipola V, Bisaccia M, Caraffa A, Barron EM, Nobile F, Cioffi R, Meccariello L. Use of Common Inflammatory Markers in the Long-Term Screening of Total Hip Arthroprosthesis Infections: Our Experience. Adv Orthop. 2017;2017:9679470. doi: 10.1155/2017/9679470. Epub 2017 Aug 23. PMID: 29138696; PMCID: PMC5613705.

Response: Thank you for this suggestion. But we would like to point out that the entire concept behind studying Interleukin 6 and serum lactate as biomarkers instead of those mentioned in the above study was because previous studies had shown that inflammatory markers such as mean platelet volume and erythrocyte sedimentation rate could not reliably predict outcomes even when used with the anatomical and physiological scoring systems. (References 6,7). Furthermore, in a study conducted in the same geographical location as ours by Douraisamy et al which was also cited in the study, it was concluded that Interleukin 6 was more specific and predicted the onset of Multiple Organ Dysfunction Syndrome earlier than CRP or PCT in patients with open fractures prone to septic shock.

Reviewer C

Comment 1: *The authors should clearly define what they mean by MODS. In other words what score was used to define a patient with MODS and when did the MODS occur? Since MODS scores are typically calculated using the same parameters as SOFA, it is surprising that MODS and SOFA did not highly correlate. This should be explained.*

Response 1: Thank you for pointing this out. We have added the definition of MODS as suggested in your review in our introduction

Page 3, Reference 5

- Multiple organ dysfunction syndrome (MODS) was defined as a condition occurring due to initial inflammatory phase following polytrauma or multiple trauma, characterized by reversible physiological abnormalities with the dysfunction of two or more organs that occurs simultaneously leading to longer stays in the intensive care unit (ICU) or mortality in severe cases. (5)
- In our study, we diagnosed the occurrence of MODS when SOFA score was **more than four on any given time** during the study period. (9) based on studies conducted previously by Lambden et al. The same has been mentioned in the methodology as suggested by you.
- We would like to point out that in our study, SOFA scores and occurrence of MODS did not significantly correlate due to the small sample size and due to the fact that the injuries sustained by the patient itself would result in deranged SOFA scores during the initial 5 days following trauma which was our study period.

Comment 2: *It would help to have a more detailed table of the patients that did or did not develop MODS. For example, more information on patient characteristics, injury characteristics (Shock Index), and outcomes including ventilator days, survival, ICU days etc.*

Response 2: We agree. We have added the above information in the form of a table in the revised document.

Table 3: Correlation between Patient's vitals, ISS, SOFA score and Multiple Organ Dysfunction Syndrome (MODS):

		MODS	NO MODS
PATIENTS (n)		4	26
AGE (Years)		40.75±8.23	44.27±2.81
SEX (M:F)		3:1	23:3
PULSE		118.5±4.99	104.88±3.29
SPO2		89.52±6.61	94.35±1.05
ISS	DAY0	44.25±3.33	30.15±1.90
	DAY1	45.75±2.25	30.52±2.15 (25)
	DAY5	46.75±1.89	29.71±2.07 (24)
SOFA Score	DAY1	3.75±1.38	1.46±0.33
	DAY2	3.25±1.44	0.96±0.22 (25)
	DAY3	2.00±1.23	0.88±0.26 (25)
	DAY4	2.00±1.23	0.46±0.19 (24)
	DAY5	2.00±0.82	0.50±0.26 (24)

Comment 3: *What were the times between injury and the first blood draw?*

Response 3: The duration between time of injury and first blood draw was an average of 180 +/- 120 minutes. The same was not included in our study because unlike studies conducted in western countries measured serial serum IL-6 levels in each individual trauma patient as early as from the scene of injury whereas in this study, the first blood draw occurred only in the Emergency department when patients reported at different times to the hospital within 24 hours following trauma.

Comment 4: *AUC should be provided for ISS alone, IL6 alone and lactate alone on admission.*

Response 4: AUC has been provided for IL-6 and serum lactate alone on admission in a new table added to the revised manuscript. (Table 5 and Fig 1) We agree with you that an AUC for ISS would have also been helpful to compare but it was not included in our study since previous studies have established fallacies in the ISS alone in predicting MODS which has led us to look for more specific bioscores as mentioned in our study.

Reviewer D:

Comment 1: *The study is predicated on the Indian subcontinent population being different. In the introduction please provide the basis for this assumption.*

Response 1: Thank you for going through our article and providing suggestions sir. With respect to the above suggestion, the reason that we feel that Indian subpopulation is different compared to western studies is mainly because most trauma patients in India are between the age groups of 20-50 years and hence have a heightened immune response when compared to subjects studied in Western countries who were mostly greater than 60 years of age.

Comment 2: In the introduction the focus is put on the definition of a polytrauma patient. While in the methods the inclusion criteria was an ISS >16. Later in the results the statement was made that “IL6 levels were higher than the normal range in all patients with polytrauma and 25% of patient with multiple trauma”. These different populations need to be defined. In addition, the populations with MODs and death need to be clarified. It is unclear what percent of the subjects died or had MODs.

Response 2: Thank you for the suggestions sir. The same has been added to our revised document.

Methodology, Page 5

- Patients with **two or more organ systems involvement** were considered as Polytrauma patients and patients with **one or more organ system involvement or patients with more than one long bone injury** were considered as Multiple trauma patients.
- The patient was considered to have developed Multiple Organ Dysfunction Syndrome (MODS) if SOFA score was more than four on any given time during the study period. (9)

Table 2

- We have included the number of patients who developed Multiple Organ Dysfunction Syndrome.
- **Table 2: Correlation between Patient’s vitals, ISS, SOFA score and Multiple Organ Dysfunction Syndrome (MODS):**

		MODS	NO MODS
PATIENTS (n)		4	26
AGE (Years)		40.75±8.23	44.27±2.81
SEX (M:F)		3:1	23:3
PULSE		118.5±4.99	104.88±3.29
SPO2		89.52±6.61	94.35±1.05
ISS	DAY0	44.25±3.33	30.15±1.90
	DAY1	45.75±2.25	30.52±2.15 (25)
	DAY5	46.75±1.89	29.71±2.07 (24)
SOFA Score	DAY1	3.75±1.38	1.46±0.33
	DAY2	3.25±1.44	0.96±0.22 (25)
	DAY3	2.00±1.23	0.88±0.26 (25)
	DAY4	2.00±1.23	0.46±0.19 (24)
	DAY5	2.00±0.82	0.50±0.26 (24)

Results Page 7

- Of the 30 patients, four patients developed MODS and two patients died during the study period.

Comment 3: Throughout the paper data is referred to that has not been presented. For example, the correlation of IL6 and lactate.

Response 3: Thank you for the suggestion sir. We have added a table showing the correlation of Interleukin 6 and Serum lactate and also their correlation with development of MODS and a correlation coefficient matrix comparing ISS, SOFA score, IL-6 and Serum lactate has also been added

Table 1 and Table 3

Table 2: Correlation of Injury Severity score, SOFA score, IL-6 and Serum lactate levels on Day 0,1 and 5

	Injury Severity Score	SOFA Score						Interleukin 6 (pg)				Serum Lactate			
Injury Severity Score	da y0	1	0.977**	0.968**	0.468	0.572*	0.658*	0.596	0.669**	0.618**	0.748**	0.609*	0.623**	0.652**	0.655**
	da y1		1	0.998**	0.489	0.525*	0.576*	0.519**	0.616	0.665**	0.807**	0.624**	0.621**	0.621**	0.655**
	da y5			1	0.466	0.467*	0.503	0.505**	0.620**	0.632	0.822**	0.624**	0.574*	0.588*	0.666**
SOFA Score	da y1				1	0.937**	0.822**	0.783**	0.611*	0.126*	0.293	0.122	0.755**	0.653**	0.557*
	da y2					1	0.888**	0.876**	0.672**	0.298*	0.447*	0.168	0.791**	0.772**	0.628**
	da y3						1	0.949**	0.842**	0.372**	0.486	0.323	0.777**	0.761**	0.679**
	da y4							1	0.893**	0.255	0.326	0.370	0.719**	0.692**	0.748**
	da y5								1	0.365**	0.446*	0.632**	0.643**	0.607*	0.819**
Interleukin 6 (pg)	da y0									1	0.904**	0.825**	0.374*	0.489*	0.485*
	da y1										1	0.701**	0.556*	0.656**	0.542*
	da y5											1	0.337	0.337	0.673**
Serum Lactate	Da y0												1	0.932**	0.852**
	Da y1													1	0.809**
	da y5														1

Table 3: Correlation between IL-6, Serum lactate and Multiple Organ Dysfunction Syndrome (MODS)

		MODS	NO MODS	SIGNIFICANCE
IL-6	DAY0	122.58±36.70	73.38±18.74	p< 0.001
	DAY1	126.43±37.18	60.83±15.88 (25)	p< 0.001
	DAY5	88.22±34.00	45.71±13.13 (24)	p< 0.001

SL	DAY 0	4.58±0.53	2.66±0.32	p< 0.001
	DAY1	4.20±0.59	2.62±0.27 (25)	p< 0.001
	DAY5	4.03±0.42	1.93±1.06 (24)	p< 0.001

Comment 4: *In the discussion the statement is made that the majority of participants had no comorbidities yet 40% of the patient were diabetic.*

Response 4: We apologise for the statement. What we meant to imply is that most patients had no comorbidities (n= 20) and among those who did, 40 % were diabetic (n=6).