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The Liver Function Score – "ALBI" Sets Apart Melioidosis, Scrub Typhus from Viral Hepatitis, Tuberculosis, Enteric Fever in a III-II Grade Score: Useful in Machine Learning and AI

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Authors' contributions

This work was carried out under ICMR funded project on Mission Melioidosis. Author SK contributed to the concept and writing of the manuscript. Subsequent review and improvement of the manuscript was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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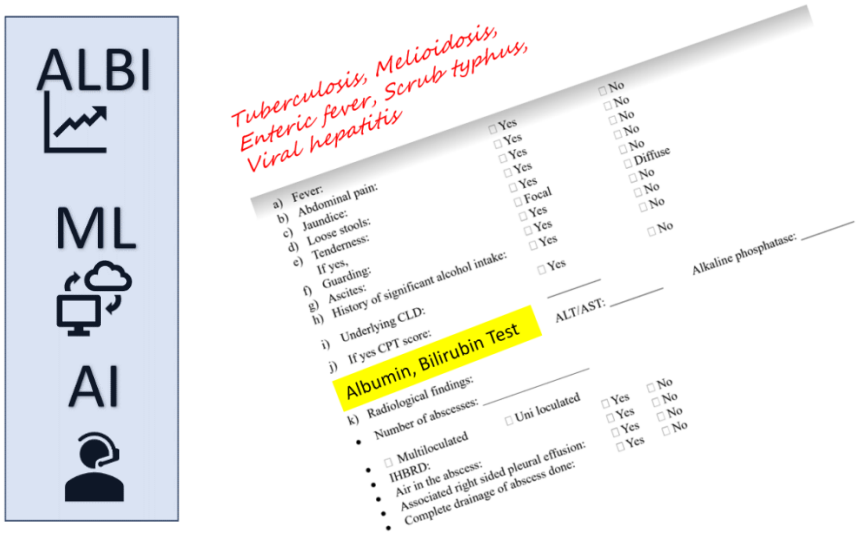
ABSTRACT

ALBI (Albumin-Bilirubin) score is routinely used in grading liver function of hepatocarcinoma and hepatitis patients. In this purposive review, the published values of serum albumin, bilirubin in Viral hepatitis, Tuberculosis, Scrub typhus, Enteric fever has been compared with that of melioidosis. Since PubMed yielded zero searches with key words “albumin, bilirubin, melioidosis”, it was searched in Google Scholar, a better retrievable search engine. This yielded 46 relevant articles with 53 ALBI scores for Melioidosis. An equivalent search to retrieve 53 ALBI scores was made in Google Scholar for other confounding diseases of Melioidosis with search words “albumin, bilirubin, hepatitis” “albumin, bilirubin, tuberculosis”, “albumin, bilirubin, scrub typhus”, “albumin, bilirubin, enteric fever”. This raw data was deposited in Harvard dataverse (https://doi.org/10.7910/DVN/QEW20J) and subsequent analysis done is documented in this article. This placed Melioidosis patients and Scrub typhus patients to be on an average grade III ALBI and the patients of Viral hepatitis, Tuberculosis, and Enteric fever in grade II ALBI.

GRAPHICAL ABSTRACT



Keywords: ALBI; melioidosis; tuberculosis; scrub typhus; enteric fever.

ABBREVIATIONS

ALBI : Albumin-Bilirubin Grade;
AI : Artificial intelligence;
ML : Machine Learning;

1. INTRODUCTION

Many infectious diseases involve hepatic dysfunction and the prominent serological markers used in prognosis are bilirubin, serum albumin, aspartate alanine transferase, gamma glutamyl transferase, alkaline phosphatase. One such disease is Viral hepatitis that is caused by infection of parenterally transferred HBV (*hepatitis B virus)*, HCV (*hepatitis C virus)*, HDV (*hepatitis D virus)* and by food borne viruses like HAV (*hepatitis A virus0*, HEV (*hepatitis E virus)*. Similar hepatic and skin involvement is observed in another infectious disease like Melioidosis [1,2]. Further it is reported that the patients with liver, splenic abscess along with skin abscess had higher chance of being Melioidosis positive (Sakulchit et al., 2021).

The common serological marker “bilirubin” is formed from the breakdown of heme molecule to biliverdinin reticuloendothelial cells, Kupfer cells by the action of mononuclear heme oxygenase, resulting in the formation of unconjugated form of bilirubin [3]. Its elimination through hepatic and renal routes occur in its hydrophilic conjugated form (bilirubin glucuronide). This form of bilirubin travels into bile, enters the intestine subsequently

to be excreted via urine as urobilinogen and via feces in the form of stercobilinogen. Jaundice is indicated by high bilirubin levels (>3mg/dl) in which pre-hepatic or hepatic jaundice refers to elevation of unconjugated bilirubin and post-hepatic jaundice refers to elevation of conjugated bilirubin [3].

Another common marker is serum albumin and these two markers (albumin, bilirubin) was used to develop a grading system to classify patients in context to the level of mortality risk these patients are into. This scoring system namely, ALBI as developed by Johnson et al., [4] that helps to assess liver function in patients with HCC (hepatocellular carcinoma), hepatitis [5,6]. ALBI scoring system for hepatitis, grades patient into grade 1, grade 2, and grade 3 based on the serum albumin and bilirubin levels. Grade 3 patients have highest risk of mortality and the score is towards positive values and the Grade 1 patients have lowest risk of mortality and score is towards negative values. However this kind of grading system is seldom published in articles on Melioidosis and other confounding diseases of Melioidosis like tuberculosis, scrub typhus, enteric fever.

Hence the objective was to conduct a literature search to retrieve articles that had information on measured albumin and bilirubin values in Melioidosis and compare it with that in viral hepatitis, tuberculosis, scrub typhus, enteric fever. This also had another importance that measurement of ALBI is economically feasible and following this model it could be applied in other diseases.

Enteric fever, a food and water borne disease is caused by *Salmonella typhi* and the common symptoms include fever, stomach upset [7]. Other confounding disease for Melioidosis includes Tuberculosis and the patients who have active infection have symptoms like appetite loss, fever, fatigue, weight loss. Tuberculosis patients with pulmonary disease have persistent cough and can cough up blood [8]. Further malnutrition, diabetes are risk factors for tuberculosis [8] that could be risk factor for Melioidosis too. Another confounder includes scrub typhus that is caused by the bacteria *Orientia tsutsugamishi* and is transmitted by the bite of mite larva [9].

Initial search in search engine like Pub Med yielded zero results and hence Google Scholar was used for drafting this purposive review. It is to be noted that, contrary to deep extraction systematic review, the purposive review captures insightful work that a systemic review could miss out but with little assurance of balanced perspective [10]. Further it is to be noted that Google Scholar has been referred to as a better retrievable search engine with equivalent precision to Pub Med and free access to articles [11].

2. METHODOLOGY

An initial search of key words “albumin, bilirubin, melioidosis” yielded zero output n Pub Med but for hepatitis it had innumerable output (Fig. 2). Hence purposive review was adopted and Google Search was used. The search was conducted between Dec 2022- March 2023. The total extractable articles were 46 with inclusion criteria of Melioidosis infection and presence of albumin, bilirubin values. The total ALBI extractable was 53 from these 46 articles. To obtain an equivalent 53 ALBI values in hepatitis, the first appearing 20 articles had 53 values of ALBI with search option of “albumin, bilirubin, hepatitis”. The inclusion criteria included articles with viral hepatitis and values of albumin, bilirubin. Similarly, search was done with key words “albumin, bilirubin, scrub typhus”, “albumin, bilirubin, tuberculosis”, albumin, bilirubin enteric fever”. The ALBI score was calculated as in Johnson et al.,[4]:

- The ALBI grade =-0.085 × (albumin in g/L) + 0.66 ×log (bilirubin in μmol /L).
- The ALBI grades include: ALBII ≤−2.60 (lowest risk of mortality);
- ALBIII > − 2.60 to≤−1.39 and ALBIIII > −1.39 (highest risk for mortality)

3. RESULTS

The raw data was deposited in Harvard dataverse (https://doi.org/10.7910/DVN/QEW20J).Out of 53 ALBI grades obtained from literature search for Melioidosis, 3 were in ALBI Grade I, 18 were in ALBI Grade II, 32 were in ALBI Grade III with an average ALBI score of -1.19 (SD 0.76). In case of viral hepatitis, 11 were in AlBI Grade 1, 27 were in Grade II, 15 were in Grade III with an average ALBI score of -1.76 (SD 0.99). In case of Tuberculosis 10 were in Grade 1, 36 were in Grade II, 7 were in Grade III with an average of -2.12 (SD 0.97). In case of Scrub typhus 0 were in Grade I, 23 were in Grade II, 30 were in Grade III with an average of -1.18 (SD 0.65). In case of enteric fever, 5 were in Grade I, 24 were in Grade II and III with an average ALBI Score of -1.58 (SD 0.81).

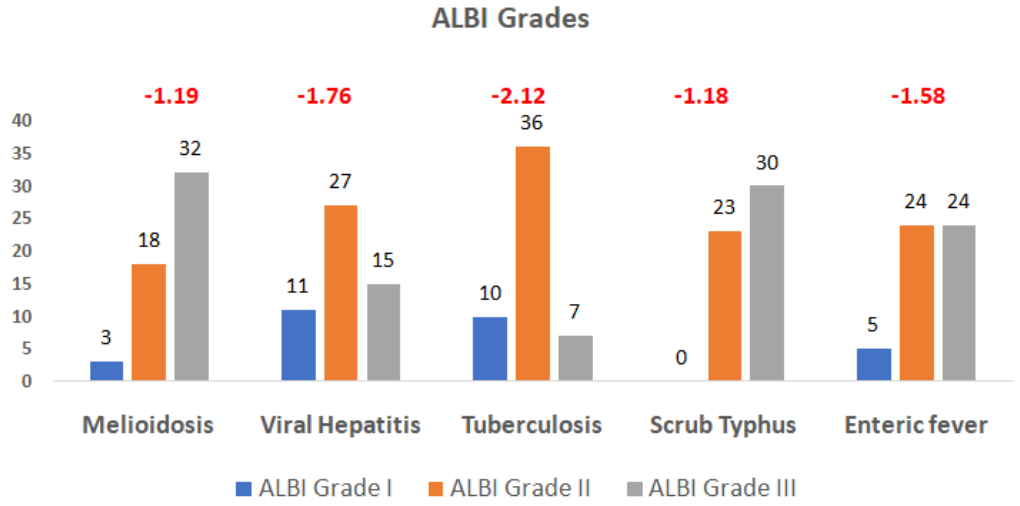


Fig. 1. ALBI Grades in different Melioidosis confounders as calculated from references [12-159]. The numbers denote the no of cases out of 53 ALBI grade scores

4. DISCUSSION

Melioidosis is a high-risk pathogen of public health importance [160].

The WHO's list on neglected tropical disease does not include Melioidosis although an appeal has been made for Melioidosis to be included in this list [161]. Since the disease also involves affected liver function, a scoring system predominantly used in viral hepatitis has been applied to this. In this article, this scoring system was extended to diseases that confound diagnosis of Melioidosis that includes tuberculosis, scrub typhus, enteric fever. As with the supporting literature, possibly, this is the first time that the ALBI is used for infectious diseases other than viral hepatitis and the other confounders.

The results of the present review indicated that average ALBI score differed significantly in Melioidosis than in viral hepatitis. Melioidosis and Scrub typhus were in average Grade III and Grade II for viral hepatitis, tuberculosis, enteric fever. It may give a preliminary idea about the involvement of liver function and may suggest acute intervention by transferring the patient to any tertiary health care center. The one other advantage of ALBI is the use of only two parameters (albumin, bilirubin) that can be economically feasible in a rural setup. This score is not the only one, but one of the most important tests that can be performed in any setting.

Since it is a purposive review and not a systematic review, the interpretation should be dealt with caution although the novel insight is to use this score in other infectious diseases. Although it is a purposive review, it does show one basic insight that ALBI is not calculated in other infectious diseases although albumin, bilirubin is measured and this could be valuable. Further such serology-based scores could be useful in machine learning and artificial intelligence as seen in many publications [162-166].

Table 1. P-Value of student T-test comparing pairs of diseases

	Viral Hepatitis	Tuberculosis	Scrub Typhus	Enteric fever
Melioidosis	0.000635723	1.67625E-07	0.472205901	0.005966564
Viral hepatitis		0.0325155	0.0002879	0.156314366
Tuberculosis			3.3032E-08	0.001343133
Scrub Typhus				0.002986919

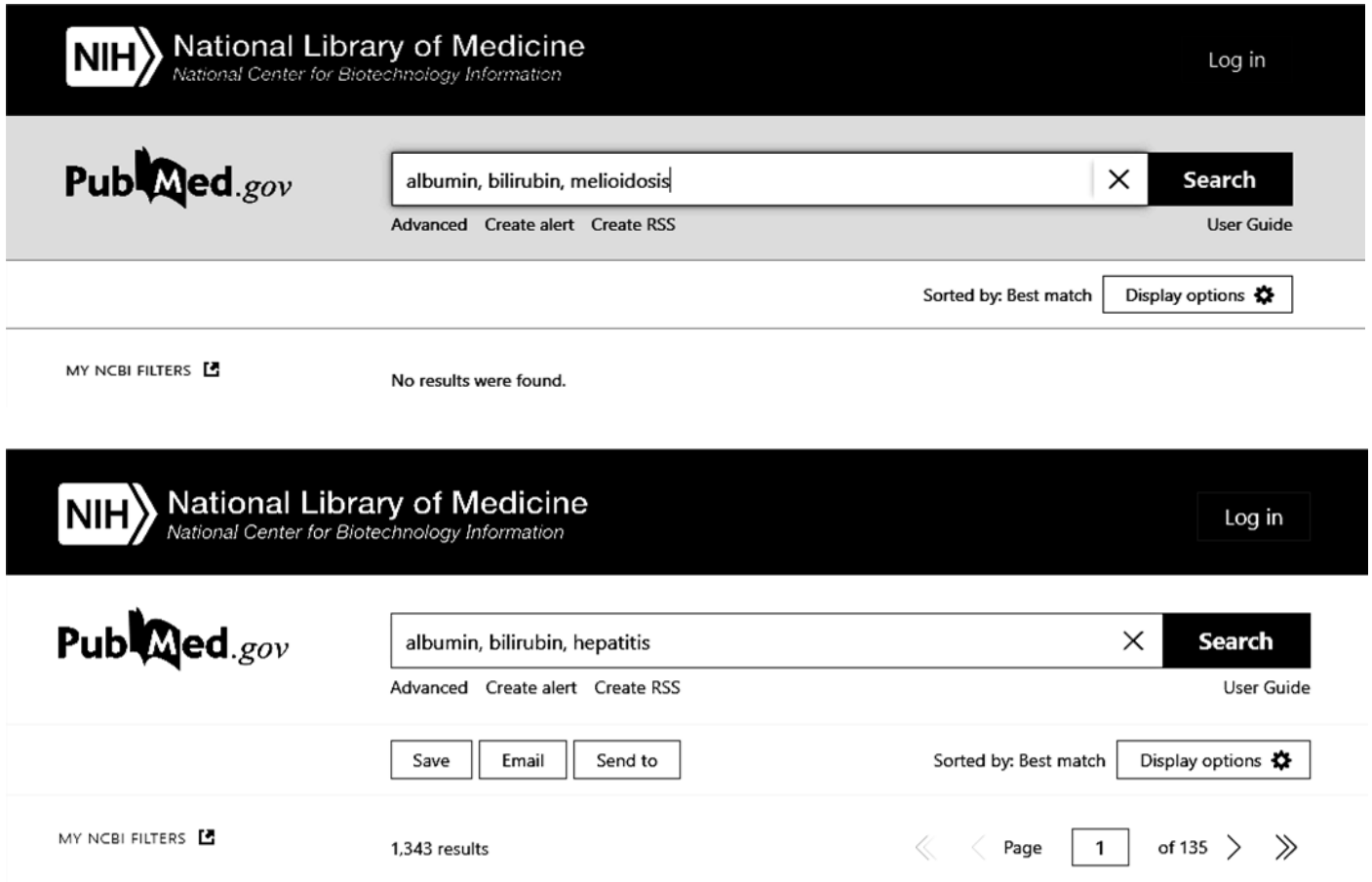


Fig. 2. Screenshot of search in Pub Med. With search options of "albumin, bilirubin, melioidosis" in Pub Med yielded zero results and with search options "albumin, bilirubin, hepatitis" yielded 1346 results

5. CONCLUSION

- The study indicated the average ALBI score calculated from 53 published albumin, bilirubin values to be significantly different in Melioidosis, scrub typhus from that of tuberculosis, viral hepatitis and enteric fever through adopting purposive review
- Since measuring ALBI is economically feasible, the future direction could be to apply it for other infectious diseases apart from viral hepatitis.

CONSENT AND ETHICAL APPROVAL

Since it is purposive review, the literature search was obtained from Google Scholar, IEC approval is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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