

**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**

## 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.

**Keywords:** ALBI, Melioidosis, Tuberculosis, Scrub typhus, Enteric fever,

### Abbreviations:

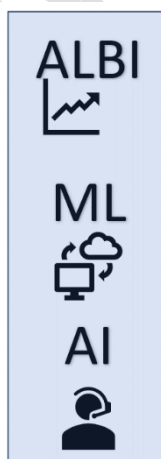
ALBI – Albumin Bilirubin score;

AI – Artificial intelligence;

ML – Machine Learning;

HBV – Hepatitis B virus; HCV- Hepatitis C virus; HAV- Hepatitis A Virus; HDV – Hepatitis D Virus

## Graphical Abstract



## Introduction

Many infectious diseases involve hepatic dysfunction and the prominent serological markers used in prognosis are bilirubin, serum albumin, aspartate alanine transferase, gammaglutamyltransferase, alkaline phosphatase. One such disease is Viral hepatitis that is caused by infection of parenterally transferred HBV, HCV, HDV and by food borne viruses like HAV, HEV. Similar hepatic and skin involvement is observed in another infectious disease like Melioidosis (Teo et al., 2006), (Rostey et al., 2015). 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 biliverdin in reticuloendothelial cells, Kupfer cells by the action of mononuclear heme oxygenase, resulting in the formation of unconjugated form of bilirubin (Joseph and Samant.,2022). 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 (Joseph and Samant., 2022).

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., 2015 that helps to assess liver function in patients with HCC (hepatocellular carcinoma), hepatitis (Demirtas et al., 2021), (Lescure et al., 2021). 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 (Mukhopadya et al.,2019). 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 (Pai et al.,2014). Further malnutrition, diabetes are risk factors for tuberculosis (Pai et al.,2014) 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 (Singh et al.,2022).

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 (Cook et al., 2019).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 (Shariff et al.,2013).

## **Methodology**

An initial search of key words “albumin, bilirubin, melioidosis” yielded zero output n Pub Med but for hepatitis it had innumerable output (**Figure 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.,2015:

$$\text{The ALBI grade} = -0.085 \times (\text{albumin in g/L}) + 0.66 \times \log (\text{bilirubin in } \mu\text{mol /L}).$$

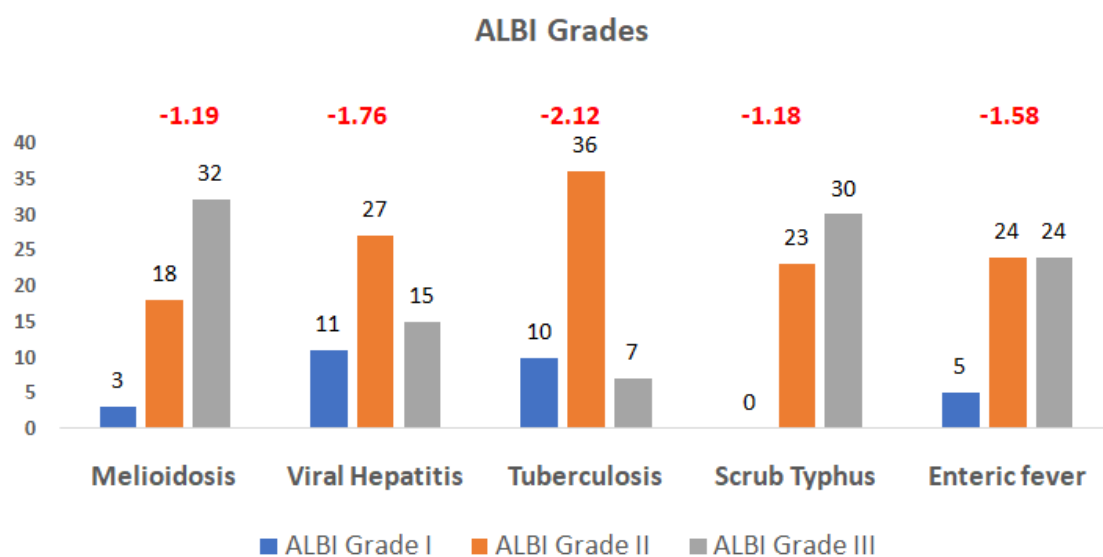
The ALBI grades include: ALBII  $\leq$  -2.60 (lowest risk of mortality);

ALBIII  $>$  - 2.60 to  $\leq$  -1.39 and ALBIII  $>$  -1.39 (highest risk for mortality)

## 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).



**Figure 1.** ALBI Grades in different Melioidosis confounders. The numbers denote the no of cases out

of 53 ALBI grade scores

	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

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

Patient	Serum albumin (g/dL)	Serum globulin (g/dL)	Serum total bilirubin (mg/dL)	Serum direct bilirubin (mg/dL)	ALBI	Grade
1	1.7	3.3	0.4	0.3	-0.89219	III
2	2.4	4.1	0.4	0.2	-1.48719	II
3	2.88	3	0.2	0.1	-2.09387	II
4	3.4	3.9	1.06	0.62	-2.05785	II
5	4	3.5	0.25	0.12	-2.98191	I
6	3.6	4.5	0.35	0.16	-2.54547	II
7	3.39	3.7	0.88	0.5	-2.10269	II

**Table 2 Melioidosis -Tuberculosis co infected Patient values from Kasturba Medical college, Manipal for validation of the hypothesis on ALBI**

## Discussion

Melioidosis is a high-risk pathogen of public health importance (Mukhopadya et al.,2013). 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 (Savelkoel et al., 2021). 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.

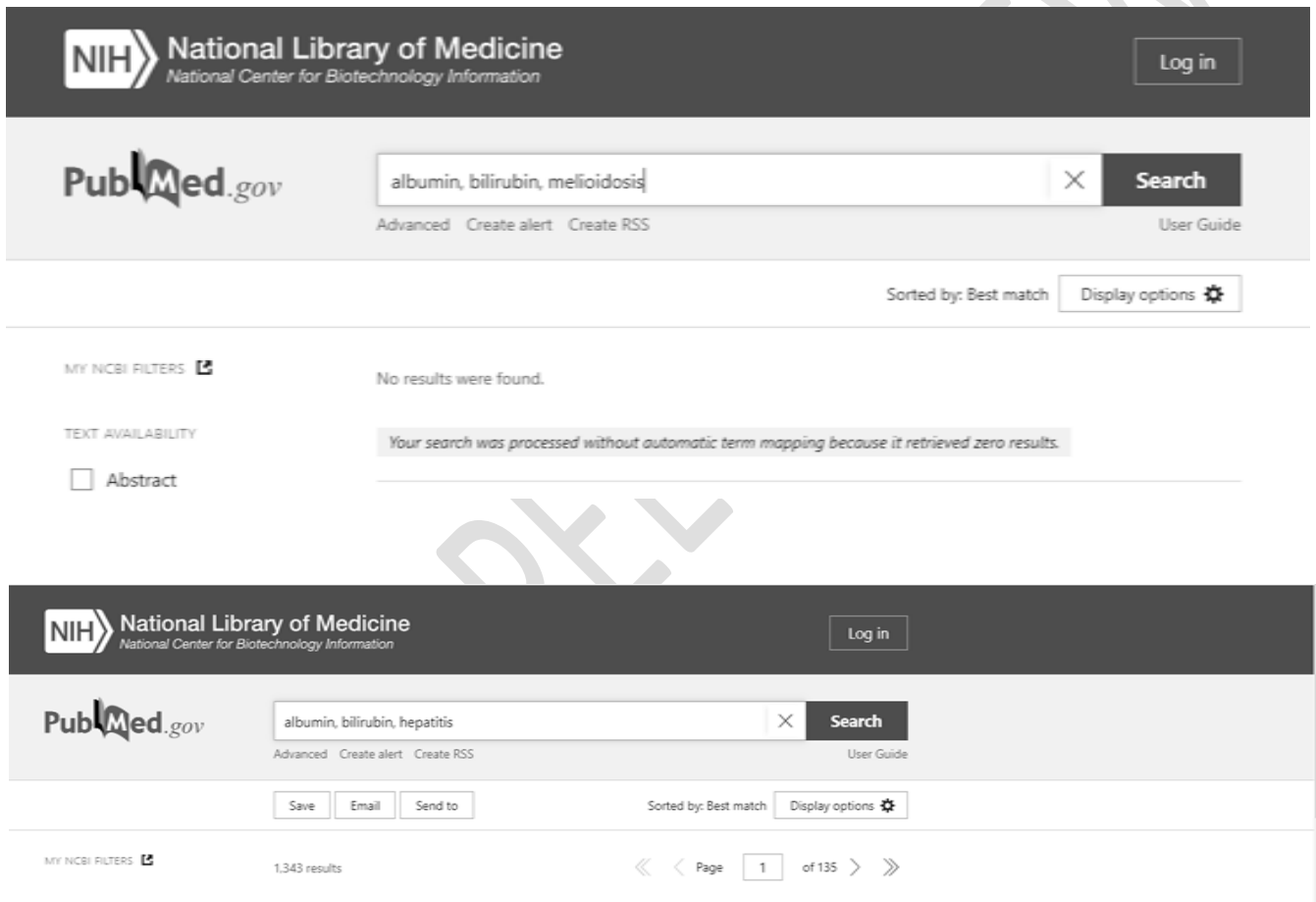
The results of the present review indicated that average ALBI score differed significantly in Melioidosis than in viral hepatitis. Melioidosis and Scrub typhus were in average Grade III and Grade II for viral hepatitis, tuberculosis, enteric fever. It may give a preliminary idea about the involvement 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.

In this article, based on literature review, the prediction is Grade 2 ALBI for tuberculosis and Grade 3 for Melioidosis and in real time data as seen in Table 2, the ALBI score in patients co infected with Melioidosis and Tuberculosis is Grade 2.

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 (Elkin et al., 2022, Zhang et al., 2021, He et al., 2021, Cuocolo et al 2020, Chaki et al., 2022).

### **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.



**Figure 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.

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