# Association of Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) with Mortality in Patients with Coronavirus Disease 2019 (COVID-19) in Fatmawati General Hospital: A Preliminary Data

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## ABSTRACT

***Background:*** *COVID-19, caused by SARS-CoV-2 virus, is a novel disease that has not been previously identified. The disease may result in multiple organ impairment leading to death. Liver is also affected by this viral infection. This study aimed to investigate the association of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with mortality rate in these patients.*

***Method:*** *This is a retrospective cohort study of COVID-19 patients admitted in Fatmawati General Hospital during a period of March-April, 2020. Diagnosis of COVID-19 was established from real time polymerase chain reaction (RT PCR). Association of AST and ALT levels with mortality was analyzed by using SPSS® version 16.0.*

***Results:*** *Forty-two patients were diagnosed as confirmed case of COVID-19, 52.3% of them were male. Mean age was 54.6 ± 12 years. Median (IQR) value of AST and ALT levels were 55(48) U/L and 39(40) U/L, respectively. AST and ALT was elevated in 71.4% and 42.9%, respectively. Increased levels of AST and ALT ≤ 2 times above the upper normal limit (UNL), >2 times ULN, and > 5 times ULN were found in 33.3% and 21.4%; 38.1% and 21.4%; 4.8% and 4.8%, respectively. Mortality was recorded in 45.1% of these confirmed cases, 50% occurred within 2 days of hospitalization. Higher mean value of AST is associated with an increased mortality risk (101 ± 147 U/L vs. 82.78 ± 173 U/L; p 0.032). Sub-analysis identified that abnormal AST >2 times above UNL has a higher mortality proportion compared with AST ≤ 2 times UNL and normal AST levels (62.5% vs. 50% vs. 16.7%; p 0.05). Mean value of ALT is not associated with mortality (p 0.479). Further sub-analysis found that in patients who succumbed to the disease, abnormal levels of AST and ALT is related to the time of death during hospitalization despite being statistically not significant.*

***Conclusion:*** *Mortality rate of COVID-19 in hospitalized patients remains high. Increased AST levels was significantly associated with higher mortality rate. This finding merit further investigation by incorporating larger sample size to discern the role of these factors' contribution to mortality in COVID-19.*

***Keywords:*** *Aspartate aminotransferase (AST), alanine aminotransferase (ALT), COVID-19, mortality*

## ABSTRAK

***Latar belakang:*** *COVID -19 adalah penyakit jenis baru yang belum pernah diidentifikasi sebelumnya. Penyakit ini menyebabkan gangguan organ dan kematian yang tinggi. Hati merupakan salah satu organ yang terdampak. Penelitian ini dilakukan untuk melihat hubungan aspartate aminotransferase (AST), alanine aminotransferase (ALT) dengan tingkat kematian.*

***Metode:*** *Dilakukan metode kohort retrospektif terhadap pasien yang didiagnosis dan dirawat sebagai COVID-19 di RSUP Fatmawati periode Maret-April 2020. COVID-19 ditegakkan dengan pemeriksaan PCR swab. Hubungan antara AST, AST dan kematian pada pasien COVID-19 dianalisa menggunakan SPSS veri 16.*

***Hasil:*** *42 orang pasien terdiagnosis COVID-19 dari PCR dirawat di RS Fatmawati dari Maret-April 2020. Lima puluh dua koma tiga persen pasien laki laki. Rerata usia pasien 54.6 ± 12 tahun. Nilai median AST dan ALT pada pasien adalah 55 (48) U/L dan 39 (40) U/L. Peningkatan AST dan ALT dtemukan pada 71.4% dan 42.9%. Peningkatan AST dan ALT 1-2xNBA, >2xNBA dan >5NBA ditemukan pada 33.3% dan 21.4%; 38.1% dan 21.4%; 4.8% dan 4.8% pasien. Pasien yang meninggal dalam perawatan ditemukan pada 45.5% pasien, 50 % dari yang meninggal terjadi ≤ 2 hari perawatan, dan 30 % dalam perawatan > 5 hari. Rerata kadar AST yang semakin tinggi memiliki risiko mortalitas yang semakin tinggi (101 ± 147 U/L vs. 82.78 ± 173 U/L; p 0.032). Dari analisa subanalisis ditemukan bahwa Kadar AST abnormal >2xNBA memiliki proporsi mortalitas lebih tinggi dibandingkan AST 1-2x NBA (>34 g/dL), dan AST 1-2xNBA memiliki proporsi mortalitas lebih tinggi dibanding AST normal (62.5% vs 50% vs 16.7%; p 0.05); Rerata kadar ALT tidak berkaitan dengan status mortalitas pasien (p 0.479). Pada subanalisis pasien yang meninggal rerata AST dan ALT yang abnormal berkaitan dengan cepatnya waktu kematian dalam perawatan meskipun secara statistik tidak ditemukan kemaknaan.*

***Simpulan:*** *Tingkat kematian pada pasien COVID-19 yang dirawat di RS masih sangat tinggi, Peningkatan kadar enzim transaminase merupakan salah satu faktor risiko yang secara bermakna berkaitan dengan kematian. Semakin tinggi nilai kadar AST semakin tinggi resiko kematian. Diperlukan studi lanjut dengan jumlah sampel lebih besar untuk mengetahui peranan lebih lanjut dari faktor faktr tersebut.*


***Kata kunci:*** *Aspartate aminotransferase (AST), alanine aminotransferase (ALT), COVID-19, mortalitas*

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease identified in December 2019. The disease is caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) originally emerged in Wuhan, China and a swift spread was subsequently observed worlwide prompting the World Health Organization (WHO) declared it as pandemic. COVID-19 was detected in Indonesia for the first time in early March 2020. Up to early May, more than 3 millions confirmed cases were reported leading to more than 250 thousands death.[1] In Indonesia according to data from the Task Force for the Acceleration of Handling COVID-19, Republic of Indonesia, up to May 7, 2020 reported 12,776 confirmed cases with 930 deaths nationwide.[2] Despite mortality rate due to SARS-CoV-2 infection is lower than other coronavirus, the virus is easily spread and may survive longer on various surfaces.[3]

Lung is the primary target organ attacked by the virus and eliciting main clinical symptoms, however it also has the capacity to affect various organs. Altogether this viral infection may lead to serious complication such as acute respiratory distress syndrome (ARDS) accompanied by multi organs failure. Around 2-10 % patients with COVID-19 presented to hospitals with gastrointestinal tract complaints such as diarrhea or abdominal pain.[4] In addtion. Presence of SARS-CoV-2 RNA has been detected in faeces and gastrointestinal tract.[4,5] This evidence suggests the possibility of viral presence in the liver and gastrointestional tract. Early study from Wuhan reported elevated liver transaminase enzymes in 20-50%.[6] However, its role on overall liver function and the impact of mortality remains controversial. Liver dysfunction in COVID-19 patients might develop from direct viral infection to liver cells or by means of host immune system mechanism. SARS-CoV-2 virus requires binding to Angiotensin-converting enzyme 2 (ACE2) receptor on target cell prior to its replication. Preliminary study demonstrated that ACE2 receptor is expressed in the cholangiocyte, possibly contributing to liver dysfunction, although post-mortem examination has not identified presence of the virus on liver tissue.[7,8]

This preliminary study is conducted to investigate Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in confirmed COVID-19

cases and their relationship with mortality. Findings from this study may provide guidance and physicians' awareness in treating patients with COVID-19.

## METHOD

This is a retrospective cohort collecting medical record data from patiens admitted and hospitalized in Fatmawati General Hospital during period of March to April 2020. Diagnosis was established from history taking, physical examination, laboratory results, imaging, and real time polymerase chain reaction (RT-PCR) amplification of SARS-Cov-2 virus from pharyngeal swab according to WHO interim guidance 20 March 2020.[9]

Demographic data was obtained as recorded in patient's chart. In patient who died during hospital care, time elapsed between admission and to the time of death was determined. Laboratory examinations were performed according to the hospital protocol that include full blood counts, c-reactive protein, AST, ALT, random blood glucose, ureum, creatinine, D-dimer, Feritin, and lactate.

Normal level is defined as AST level is ≤ 34U/L while ALT ≤ 40 U/L. Demographic characteristics and examination results are presented in frequency table for categorical data and mean/median for numerical data. Association with mortality was analysed by using Chi-square Test or Fisher Rank Test on categorical variable, and using unpaired T-test or Mann U-Whitney Test for numerical data. This study has been approved by Hospital Ethical Commitee No. DM 01.01/ VIII.2/4443/2020.

## RESULTS

From 191 patients admitted for suspicion of COVID-19, 42 patients met the inclusion criteria as confirmed cases from RT PCR pharyngeal swab examined from 2 separate samplings. More than halve of these patients (52.3%) were male with mean age of 54.6 ± 12 years. According to age group, almost two thirds (64.3%) are within 30-59 years-old age group, and another 33.3% are within age group 60 years old and above.

Laboratory examination on admission revealed that mean leukocyte was 7,648 ± 3,761/uL, median lymphocyte percentage, neutrophils lymphocyte ratio (NLR), and C-reactive protein (CRP) were 12 (min 3-max 36)%, 6.25 (min 1.47-max 30,6), 7.5 (min 0.9-max 29) mg/L, respectively. Median AST and ALT were 55 (min 10-max872) U/L and 39 (min 6-max 711) U/L, respectively.

**Table. 1 Baseline characteristics**

| Variable | n (%) |
|---|---|
| Sex | |
| Male | 23 (54.8) |
| Female | 19 (45.2) |
| Age (years old) | |
| 18-29 | 1 (2.4) |
| 30-59 | 27 (64.3) |
| ≥ 60 | 14 (33.3) |
| Status on discharge | |
| alive | 23 (54.8) |
| deceased | 19 (45.2) |
| Number of days spent until death | |
| ≤ 2 days | 10 (52.6) |
| 1-5 days | 4 (21.1) |
| >5 days | 5 (26.3) |
| AST | |
| > 2 times UNL | 16 (38.1) |
| AST >1-2x UNL | 14 (33.3) |
| Normal | 12 (28.6) |
| ALT | |
| Elevated | 18 (42.9) |
| Normal | 24 (57.1) |
| ALT | |
| > 2 times UNL | 9 (21.4) |
| ALT >1-2x UNL | 9 (21.4) |
| Normal | 24 (57.1) |
| Blood Sugar > 140 mg/dL | |
| Yes | 17 (53.1) |
| No | 15 (48.9) |
| Renal Insuficiency (Cr > 1.5) | |
| Yes | 7 (17.5) |
| No | 33 (82.5) |

AST: aspartate aminotransferase, ALT: alanine aminotransferase

**Table 2. Baseline characteristics**

| Variabel | Mean (SD)/median (IQR) |
|---|---|
| Age (years) | 54.9±11 |
| Leucocyte (/uL) | 7648±3761 /uL |
| Thormbocyte /uL) | 234000 (86000) |
| Lymphocyte (/uL) | 12 (19) |
| Neutrophil to lymphocyte Ratio | 6.25(7) |
| C-Reactive Protein mg/dL) | 6 (12.2) |
| Random Blood Glucose (g/dL) | 141 (min 80 max 332) |
| AST (U/L) | 55 (min 10-max872) |
| ALT (U/L) | 39 (min 6-max 711) |
| D- dimer (ng/mL) | 2750(3363) |
| Lactate | 2.5(1) |
| Feritin *ng/mL) | 1128±827 satuan |

AST: aspartate aminotransferase, ALT: alanine aminotransferase

AST elevation was documented in 71.4% patients while ALT was elevated in 42.9%. Of all patients, AST increase ≤ 2 time above UNL occurred in 33.3% and AST increase > 2 times above upper normal limit (UNL) were found in another 38% patients. By contrast, ALT increase were similar for both group i.e. those ≤ 2 time and > 2 times above UNL ( 21.4%).

Mortality in hospitalized COVID-19 patients in this preliminary report was found to be 45.5%. Half of mortality occurred within 2 days from admission and another 30% after 5 days of hospitalization. Higher

**Table 3. Bivariate analysis**

| | Deceased n (%) | Alive n (%) | RR | 95% CI | p |
|---|---|---|---|---|---|
| Abnormal AST | | | | | |
| Yes | 17 (56.7) | 13 (43.4) | 3.4 | 0.924 - 12.517 | p.019 |
| No | 2 (16.7) | 10 (83.3) | | | |
| AST > 2 x UNL | 10 (62.5) | 6 (37.5) | 3.75 | 1.01-14.05 | p 0.015 |
| AST>1-2x UNL | 7 (50) | 7 (50) | 3 | 0.76-11.80 | p 0.075 |
| AST Normal | 2 (16.7) | 10 (83.3) | | | |
| Abnormal ALT | | | | | |
| Yes | 10 (55.6) | 8 (44.4) | 1.481 | 0.76-2.87 | p > 0.05 |
| No | 9 (37.5) | 15 (62.5) | | | |
| ALT> 2 x UNL* | 4 (44.4) | 5 (55.6) | 1.19 | 0.48-2.89 | p > 0.05 |
| ALT>1-2x UNL* | 6 (66.7) | 3 (33.3) | 1.78 | 0.89-3.56 | p > 0.05 |
| ALT Normal | 9 (37.5) | 15 (62.5) | | | |

AST: aspartate aminotransferase, UNL: upper normal limit, ALT: alanine aminotransferase

mean AST correspond to higher mortality (101±147 vs. 82.78±173; p 0.032) and abnormal AST levels is associated with higher risk for mortality i.e. Risk Ratio (RR) 3.4 (95% CI: 0.924 - 12.517). Subanalysis demonstrated higher mortality proportion occurred as AST level increased, being AST > 2 times UNL higher than those of 2 times UNL as compared with those of normal levels (62.5% vs. 50% vs. 16.7%; p = 0.05).

Although ALT levels are not associated with mortality status (p = 0.479), a higher mortality proportion is observed in subjects with abnormal ALT levels (55.6% vs. 37.5%) with an RR of 1.48 was found (95% CI: 0.765-2.87). When subanalysis performed, the highest mortality proportion was found in subjects with an ALT increase of ≤ 2 times UNL

## DISCUSSION

This preliminary study found that COVID-19 infection admitted to our hospitals occurred predominantly in male and older ages. Similar observations were reported in studies from China.[10,11,12] Mortality rate in patients hospitalized in Fatmawati Tertiary General Hospital documented from this early data is substantially higher than expected (45.1%), exceeding both national and regional of Jakarta province mortality rates i.e. 6.3% and 8%, respectively.[13] However, further analysis revealed that more than half of this death occurred within 48 hours of admission. This may be due to the fact that our hospital served as a tertiary referral, receiving severe cases with multiple comorbidities.

Mortality in COVID-19 is related to various factors among other is liver dysfunction. In other corona virus infection such as Middle East resiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), liver dysfunction has been associated with mortality.[14] However, similar association in COVID-19 remains to be elucidated with further investigation.

Liver dysfunciton in COVID-19 has been reported by Chen et al in 99 patients in Wuhan. The study reported increase in AST, ALT, and lactate dehydrogenase (LDH) in 43.4% patients, mostly mild and only found 1 case with extreme elevation (1,445 U/L dan 7,590 U/L).[10] A cohort study in China found correlation between abnormal liver function and degree of severity in COVID-19. In this cohort of 1,099 patients, AST and ALT elevation was found in 29.4% and 28.1% patients, respectively. Mean AST, ALT, and bilirubin levels is significantly higher in severe cases compared to control.[15]

This study affirms similar observation of elevated transaminase enzymes in our hospitalized patients in whom 71.4% had AST elevation and 42.9% had ALT elevation. Comparably, predominant AST elevation (21.6%) as compared to ALT (18.2%) was also documented in a study from China.[16] Meanwhile, Zhang et al reported 2-11% patients with COVID-19 had liver disease as comorbidity, and AST and ALT elevation was documented in 14-53% cases.[17]

Increase in AST level correspond to an increase in mortality rate that is statistically significant. Individuals with elevated AST level (> 34 U/L) have higher risk of mortality compared to those within normal limits (RR = 3.4; 95% CI: 0.924 - 12.517). When subanalysis was performed, it was found that RR of mortality escalates as AST level increases. Compared to normal, individuals with an increase of ≤ 2 times UNL have an RR = 3 (95% CI: 0.76-11.80; p 0.075); while in those with an increase of > 2 times UNL, a higher RR was documented (RR 3.75; 95% CI 1.01-14.05; p 0.015. Case severity might contribute to higher proportion of abnormal liver function as reported by Guan et al that documented elevated ALT level in 18.2% of patients with mild symptoms compared to 39.4% of patients with severe COVID-19. Huang et al also found similar

findings that liver dysfunction was more predominant severe cases in ICU patients (62% vs. 25%).[11]

Elevation in transaminase levels in COVID-19 patients may be due to either direct injury caused by the virus or other extrahepatic conditions.[18] This particularly may explain an increase in AST levels. Different from AST, in this study we found no statistically significant association between ALT and mortality. In patients with increased ALT level has higher RR compared to those with normal level, albeit not statistically significant. This may indicate that SARS-CoV-2 virus does not cause direct injury to liver cells. Furthermore, elevated transaminase particularly AST also relates to inflammation process affecting other organs such as myocyte and myocardium which may partly explain this more frequent increase in AST rather than ALT, being more specific to liver cells. From subanalysis, both elevated AST and ALT levels suggests a relationship with the time of death although no statistical siginificance was found.

Zhang et al reported similar findings in 82 cases of COVID-19 who succumbed to the disease during hospital care. The study reported that median time from first onset to death is 15 days (IQR 15-20) dan significant association of AST ($p = 0.002$) and ALT ($p = 0.037$) with mortality.[19] Apart from liver dysfunction, in patients with COVID-19 who died during hospitalization multiorgan failure were frequently encountered.

This is caused by viral infection per se and cytokines released as host response to the virus.[18] Several studies affirms the role of Angiotensin Converting Enzim-2 (ACE-2) in the pathogenesis of COVID-19.[4] Although 60% of cholangocytes expressed ACE-2, its proportion in hepatocytes is extremely low (2.6%). Hence injury to the biliary system is more likely to occur rather than to liver parenchyma. In COVID-19, increased levels of inflammatory cytokines are observed including IL-1 and TNF alpha.[20] An upsurge of inflammatory cytokines may result in elevated transaminase levels particularly in a severe clinical condition.[20] High CRP level is also associated with transaminase elevation.[16] Our data suggests a weak but significant correlation between CRP and AST (Correlation coefficient of 0,495, p 0.001).

Liver damage might not occur solely attributable to direct injury by the viral insult Liu et al suggested that association between COVID-19 and liver dysfunction may arise from both inflammation response towards the infection and drugs' adverse effects of drugs from a multicenter study. Therefore AST and ALT monitoring is essentials during hospital care.[15]

Limitation of the study is that it involves small sample size. Further invetigation is required incorporating larger sample size prospectively to observe causal relationship between transaminase enzymes and mortality in patients with COVID-19.

## CONCLUSION

Mortality rate of COVID-19 in hospitalized patients remains high in this preliminary data and elevated level of transaminase enzyme is one of the risk factors associated with death. Increased AST levels was significantly associated with higher mortality rate while increased ALT levels may suggest similar relationship but without statistical significance. This finding merit further investigation by incorporating larger sample size to discern the role of these factors' contribution to mortality in COVID-19.

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