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Letter to Editor

# What Does the Meta-Analysis Tell Us about Aspirin and COVID Survival?: Aspirin and COVID-19 Mortality.

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The coronavirus disease, which started in Wuhan, China in 2019, has raised many concerns about the mortality of infected patients. Besides, patients require intensive care (critically ill), and different intubation rates increase this concern [1]. One of the most important issues is the discovery of effective medications or techniques for preventing patient mortality. It is claimed that aspirin (acetylsalicylic acid, short form ASA) can reduce the likelihood of COVID-19 mortality. This was proved by several meta-analyses [3–7]. However, the results of the study by Salah and Jawahar [2] did not confirm any significant association between aspirin use and reduced mortality risk. COVID-19 can produce inflammatory agents, which can then result in a cytokine storm (interleukin 6, 8, 10, tumor necrosis factor alpha [TNF-], interferon y [IFN-]). Also, cytokine storm using various cellular mechanisms can cause blood clots (thrombosis) formation in blood vessels (such as the pulmonary capillaries) that lead to dire consequences of the disease. Complications such as acute renal failure, respiratory distress syndrome, and organ failure are considered clinically significant and can eventually lead to the death of patients. A review of meta-analyzes conducted in 2021 was performed and the results are summarized as follows (Table 1). All 6 meta-analyses were entered into a final analysis (not adjusted) and the findings were reported.

**Table 1- summary of meta-analyses and final outcomes**

| Author/s | Total cases | $\tau 2$ | I2 | RR (CI95%) | P value | Final findings |
|---|---|---|---|---|---|---|
| Salah and Jawahar [2] | 203 ASA (*E=46) 851 non-ASA (E=156) | 0.00 | 0% | 1.12 (0.84– 1.5) | 0.81 | There is no link between aspirin and COVID19 mortality. |
| Srivastava and Kumar [3] | 13705 ASA (E=531) 42991 non-ASA (E=2227) | - | 17% | 0.71 (0.64–0.78) | 0.29 | Patients in the aspirin group seem to be less likely to expire due to COVID-19 in comparison to patients in the non-aspirin group. |
| Wijaya et al [4] | 8322 ASA (E=404) | - | 69.4% | 0.54 (0.37–0.79) | 0.003 | Aspirin use seems to reduce the mortality of COVID-9 patients. |

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|---|---|---|---|---|---|---|
| | 26093 non-ASA (E=1218) | | | | | |
| Martha et al [5] | 6715 ASA (E=360) 6824 non-ASA (E=797) | 0.04 | 36.17% | 0.46 (0.35–0.61) | 0.15 | Low-dose aspirin regimens are associated with lower COVID-19 patient mortality. |
| Savarapu et al [6]** | 9570 ASA (E=548) 22392 non-ASA (E=953) | 0.05 | 47% | 0.47 (0.35–0.63) | <0.005 | Aspirin use can reduce both overall and hospital mortality from COVID-19. |
| Moore et al [7] | 14989 ASA (E=1473) 15857 non-ASA (E=1948) | 0.33 | 94% | OR=0.63 (0.40– 0.99) | <0.005 | It appears that using aspirin may be connected with a decreased risk of mortality in COVID-19. Based on the findings of the Recovery Study, it is better to continue aspirin in patients who have a non-COVID indication, but it may be worthless to add it if they don't. |

*Event(death), **All anticoagulants, aspirin and direct oral anticoagulants are included

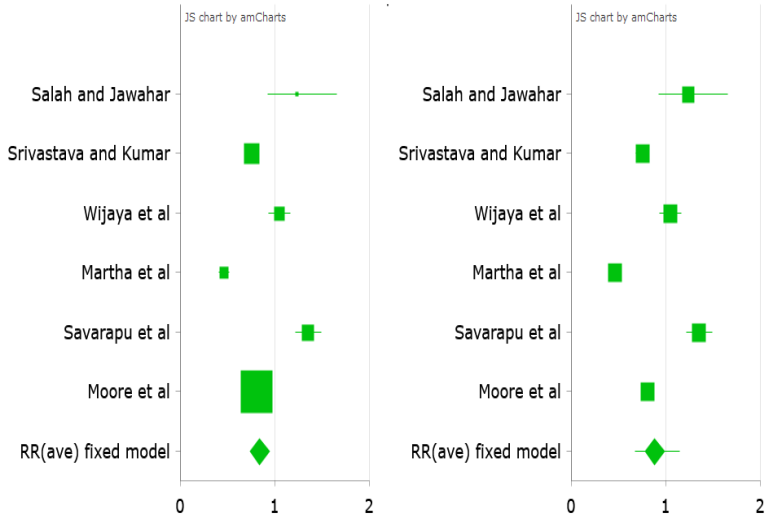
The findings of meta-analyses have some degree of overlap, and therefore the findings are random effects (not standard, fixed or adjusted). The Mantel-Haenszel risk ratio was computed, along with its 95 percent confidence intervals. Cochran's Q and I2 indices were employed to estimate heterogeneity. An I2 index less than 30% was regarded low, an I2 index between 30% and 90% was deemed moderate, and an I2 index greater than 90% was considered high. The heterogeneity of previous studies ranged from 0 to 94%. The cumulative mortality of all studies (not adjusted) was 6.28% in patients who received aspirin and 6.34% in patients who did not receive it. The relative risk was greater than one in a study by Salah and Jawahar [2].

**Table 2- Summary of results - fixed and random effect models**

| **Results based on Risk Ratio** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Ln (Risk Ratio average) | Risk Ratio average | SE | 95%CI | z score | p value | Heterogeneity |
| Fixed Effect Model | -0.17 | 0.84 | 0.02 | [0.807,0.874] | 8.542 | <.05 | I2=97.6%, Chi2=208.733, df=5 |
| Random Effect Model | -0.13 | 0.88 | 0.141 | [0.666,1.154] | 0.938 | 0.348412 | 97.6%, Tau2=0.113 |
| Results based on Odds Ratio | | | | | | | |
| Fixed Effect Model | -0.19 | 0.83 | 0.022 | [0.792,0.864] | 8.531 | <.05 | I2=97.6%, Chi2=211.859, df=5 |
| Random Effect Model | -0.14 | 0.87 | 0.153 | [0.642,1.17] | 0.935 | 0.34963 | 97.6%, Tau2=0.133 |

In the final model, I2 index was 97.6%, suggestive of considerable heterogeneity. The findings of this study reveal an association between aspirin use and death in COVID-19 patients. Relative risk (RR) and odds ratio were 0.84 and 0.83 respectively ($p<0.05$). It can be interpreted that exposure to aspirin use can reduce the risk of death due to COVID-19. The findings were statistically significant for fixed effect model and random model was not statically significant ($p>.05$). Overlapping results from previous studies can reduce the accuracy of this study.

**Figure 1- Forest plot - fixed and random effect models**




In conclusion, it seems that aspirin can be a cheap, available, and safe medication to reduce the hospital mortality of COVID-19 patients. The timing of aspirin initiation (or prescription) and the dosage of aspirin to reduce COVID-19 mortality are unknown. The role of DOACs as COVID-19 treatment should be clarified. Also, it is still unknown whether aspirin is beneficial for critically ill patients or not. If so, what proportion of patients reduce the risk of mechanical ventilation?

The important point about these findings is that patients often received extensive trials and treatments. Therefore, the studied communities were not homogeneous. Therefore, the findings of previous studies cannot be attributed exclusively to the effect of aspirin. Although some studies have tried to adjust (fix) patients based on different categories, these results still do not have enough effect to prove causal relationships.

The findings are assigned for research purposes only and should not be used as treatment or clinical judgment. Any medication prescription should be according to physician diagnosis and the adverse effects of self-medication are self-evident. Any comments from clinical researchers, medical specialists, or scientists would be highly appreciated.

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