

Supplementary

Is N-acetylcysteine Effective in Treating Patients with Coronavirus Disease 2019? A Meta-analysis

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Table 1. Detailed search strategy

Database	Query
PubMed	((((("COVID-19"[Mesh]) OR ("COVID-19/analysis"[Mesh] OR "COVID-19/complications"[Mesh] OR "COVID-19/therapy"[Mesh])) OR "SARS-CoV-2"[Mesh]) OR ("SARS-CoV-2/analysis"[Mesh] OR "SARS-CoV-2/drug effects"[Mesh]) OR "COVID-19"[TIAB] OR " COVID 19"[TIAB] OR "SARS-CoV-2 Infection"[TIAB] OR "SARS CoV 2 Infection"[TIAB] OR "SARS-CoV-2 Infections"[TIAB] OR "2019 Novel Coronavirus Disease"[TIAB] OR "2019 Novel Coronavirus Infection"[TIAB] OR "2019-nCoV Disease"[TIAB] OR "2019 nCoV Disease"[TIAB] OR "2019-nCoV Diseases"[TIAB] OR "COVID-19 Virus Infection"[TIAB] OR "COVID 19 Virus Infection"[TIAB] OR "COVID-19 Virus Infections"[TIAB] OR "Coronavirus Disease 2019"[TIAB] OR "Coronavirus Disease-19"[TIAB] OR "Coronavirus Disease 19"[TIAB] OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection"[TIAB] OR "SARS Coronavirus 2 Infection"[TIAB] OR "COVID-19 Virus Disease"[TIAB] OR "COVID 19 Virus Disease"[TIAB] OR "2019-nCoV Infection"[TIAB] OR "2019 nCoV Infection"[TIAB] OR "2019-nCoV Infections"[TIAB] OR "COVID-19 Pandemic"[TIAB] OR "COVID 19 Pandemic"[TIAB] OR "COVID-19 Pandemics"[TIAB] OR "SARS Coronavirus 2"[TIAB] OR "Coronavirus Disease 2019 Virus"[TIAB] OR "2019 Novel Coronavirus"[TIAB] OR "2019 Novel Coronaviruses"[TIAB] OR "Wuhan Seafood Market Pneumonia Virus"[TIAB] OR "SARS-CoV-2 Virus"[TIAB] OR "SARS CoV 2 Virus"[TIAB] OR "SARS-CoV-2 Viruses"[TIAB] OR "2019-nCoV"[TIAB] OR "COVID-19 Virus"[TIAB] OR "COVID 19 Virus"[TIAB] OR "COVID-19 Viruses"[TIAB] OR "Wuhan Coronavirus"[TIAB] OR "COVID19 Virus"[TIAB] OR "COVID19 Viruses"[TIAB] OR "Severe Acute Respiratory Syndrome Coronavirus 2" [TIAB] OR "COVID-19" OR "COVID 19" OR "SARS-CoV-2 Infection" OR "SARS CoV 2 Infection" OR "SARS-CoV-2 Infections" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease" OR "2019 nCoV Disease" OR "2019-nCoV Diseases" OR "COVID-19 Virus Infection" OR "COVID 19 Virus Infection" OR "COVID-19 Virus Infections" OR "Coronavirus Disease 2019" OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection" OR "SARS Coronavirus 2 Infection" OR "COVID-19 Virus Disease" OR "COVID 19 Virus Disease" OR "2019-nCoV Infection" OR "2019 nCoV Infection" OR "2019-nCoV Infections" OR "COVID-19 Pandemic" OR "COVID 19 Pandemic" OR "COVID-19 Pandemics" OR "SARS Coronavirus 2" OR "Coronavirus Disease 2019 Virus" OR "2019 Novel Coronavirus" OR "2019 Novel Coronaviruses" OR "Wuhan Seafood Market Pneumonia Virus" OR "SARS-CoV-2 Virus" OR "SARS CoV 2 Virus" OR "SARS-CoV-2 Viruses" OR "2019-nCoV" OR "COVID-19 Virus" OR "COVID 19 Virus" OR "COVID-19 Viruses" OR "Wuhan Coronavirus" OR "COVID19 Virus" OR "COVID19 Viruses" OR "Severe Acute Respiratory Syndrome Coronavirus 2") AND ("Acetylcysteine"[Mesh] OR "Acetylcysteine/pharmacology"[Mesh] OR "Acetylcysteine/therapeutic use"[Mesh] OR "N-Acetyl-L-cysteine"[TIAB] OR "N Acetyl L

























	cysteine"[TIAB] OR "N-Acetylcysteine"[TIAB] OR "NAC AL"[TIAB] OR "Acetylcysteine Sodium"[TIAB] OR "Acetylcysteine Zinc"[TIAB] OR "Acetylcysteine"[TIAB] OR "N-Acetyl-L-cysteine" OR "N Acetyl L cysteine" OR "N-Acetylcysteine" OR "NAC AL" OR "Acetylcysteine Sodium" OR "Acetylcysteine Zinc" OR "Acetylcysteine")
Embase	('coronavirus disease 2019'/exp OR 'covid 19' OR 'sars-cov-2 infection' OR 'sars cov 2 infection' OR 'sars-cov-2 infections' OR '2019 novel coronavirus disease' OR '2019 novel coronavirus infection' OR '2019-ncov disease' OR '2019 ncov disease' OR '2019-ncov diseases' OR 'covid-19 virus infection' OR 'covid 19 virus infection' OR 'covid-19 virus infections' OR 'coronavirus disease-19' OR 'coronavirus disease 19' OR 'severe acute respiratory syndrome coronavirus 2 infection' OR 'sars coronavirus 2 infection' OR 'covid-19 virus disease' OR 'covid 19 virus disease' OR '2019-ncov infection' OR '2019 ncov infection' OR '2019-ncov infections' OR 'covid-19 pandemic' OR 'covid 19 pandemic' OR 'covid-19 pandemics' OR 'sars coronavirus 2' OR 'coronavirus disease 2019 virus' OR 'novel coronavirus' OR '2019 novel coronaviruses' OR 'wuhan seafood market pneumonia virus' OR 'sars-cov-2 virus' OR 'sars cov 2 virus' OR 'sars-cov-2 viruses' OR '2019 ncov' OR 'covid-19 virus' OR 'covid 19 virus' OR 'covid-19 viruses' OR 'wuhan coronavirus' OR 'covid19 virus' OR 'covid19 viruses' OR 'severe acute respiratory syndrome coronavirus 2'/exp) AND ('acetylcysteine'/exp OR 'n acetyl l cysteine' OR 'acetyl l cysteine' OR 'n acetylcysteine' OR 'nac al' OR 'acetylcysteine sodium' OR 'acetylcysteine zinc')
Web of Science	TS=((("COVID-19" OR "COVID 19" OR "SARS-CoV-2 Infection" OR "SARS CoV 2 Infection" OR "SARS-CoV-2 Infections" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease" OR "2019 nCoV Disease" OR "2019-nCoV Diseases" OR "COVID-19 Virus Infection" OR "COVID 19 Virus Infection" OR "COVID-19 Virus Infections" OR "Coronavirus Disease 2019" OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection" OR "SARS Coronavirus 2 Infection" OR "COVID-19 Virus Disease" OR "COVID 19 Virus Disease" OR "2019-nCoV Infection" OR "2019 nCoV Infection" OR "2019-nCoV Infections" OR "COVID-19 Pandemic" OR "COVID 19 Pandemic" OR "COVID-19 Pandemics" OR "SARS Coronavirus 2" OR "Coronavirus Disease 2019 Virus" OR "2019 Novel Coronavirus" OR "2019 Novel Coronaviruses" OR "Wuhan Seafood Market Pneumonia Virus" OR "SARS-CoV-2 Virus" OR "SARS CoV 2 Virus" OR "SARS-CoV-2 Viruses" OR "2019-nCoV" OR "COVID-19 Virus" OR "COVID 19 Virus" OR "COVID-19 Viruses" OR "Wuhan Coronavirus" OR "COVID19 Virus" OR "COVID19 Viruses" OR "Severe Acute Respiratory Syndrome Coronavirus 2") AND ("N-Acetyl-L-cysteine" OR "N Acetyl L cysteine" OR "N-Acetylcysteine" OR "NAC AL" OR "Acetylcysteine Sodium" OR "Acetylcysteine Zinc" OR "Acetylcysteine"))
Scopus	(TITLE-ABS-KEY("COVID-19" OR "COVID 19" OR "SARS-CoV-2 Infection" OR "SARS CoV 2 Infection" OR "SARS-CoV-2 Infections" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease" OR "2019 nCoV Disease" OR "2019-nCoV Diseases" OR "COVID-19 Virus Infection" OR "COVID 19 Virus Infection" OR "COVID-19 Virus

	<p>Infections" OR "Coronavirus Disease 2019" OR "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection" OR "SARS Coronavirus 2 Infection" OR "COVID-19 Virus Disease" OR "COVID 19 Virus Disease" OR "2019-nCoV Infection" OR "2019 nCoV Infection" OR "2019-nCoV Infections" OR "COVID-19 Pandemic" OR "COVID 19 Pandemic" OR "COVID-19 Pandemics" OR "SARS Coronavirus 2" OR "Coronavirus Disease 2019 Virus" OR "2019 Novel Coronavirus" OR "2019 Novel Coronaviruses" OR "Wuhan Seafood Market Pneumonia Virus" OR "SARS-CoV-2 Virus" OR "SARS CoV 2 Virus" OR "SARS-CoV-2 Viruses" OR "2019-nCoV" OR "COVID-19 Virus" OR "COVID 19 Virus" OR "COVID-19 Viruses" OR "Wuhan Coronavirus" OR "COVID19 Virus" OR "COVID19 Viruses" OR "Severe Acute Respiratory Syndrome Coronavirus 2") AND TITLE-ABS-KEY("N-Acetyl-L-cysteine" OR "N Acetyl L cysteine" OR "N-Acetylcysteine" OR "N Acetylcysteine" OR "NAC AL" OR "Acetylcysteine Sodium" OR "Acetylcysteine Zinc" OR "Acetylcysteine"))</p>
Cochrane Library	<p>ID Search</p> <p>#1 MeSH descriptor: [COVID-19] explode all trees</p> <p>#2 MeSH descriptor: [COVID-19] explode all trees and with qualifier(s): [complications - CO, therapy - TH]</p> <p>#3 MeSH descriptor: [SARS-CoV-2] explode all trees</p> <p>#4 MeSH descriptor: [SARS-CoV-2] explode all trees and with qualifier(s): [drug effects - DE]</p> <p>#5 COVID-19</p> <p>#6 COVID 19</p> <p>#7 SARS-CoV-2 Infection</p> <p>#8 SARS CoV 2 Infection</p> <p>#9 SARS-CoV-2 Infections</p> <p>#10 2019 Novel Coronavirus Disease</p> <p>#11 2019 Novel Coronavirus Infection</p> <p>#12 2019 nCoV Disease</p> <p>#13 COVID-19 Virus Infection</p> <p>#14 COVID 19 Virus Infection</p> <p>#15 COVID-19 Virus Infections</p> <p>#16 Coronavirus Disease 2019</p> <p>#17 Coronavirus Disease-19</p> <p>#18 Coronavirus Disease 19</p> <p>#19 Severe Acute Respiratory Syndrome Coronavirus 2 Infection</p> <p>#20 SARS Coronavirus 2 Infection</p> <p>#21 COVID-19 Virus Disease</p> <p>#22 COVID 19 Virus Disease</p>

#23	2019 nCoV Infection
#24	COVID-19 Pandemic
#25	COVID 19 Pandemic
#26	COVID-19 Pandemics
#27	SARS Coronavirus 2
#28	Coronavirus Disease 2019 Virus
#29	2019 Novel Coronavirus
#30	2019 Novel Coronaviruses
#31	Wuhan Seafood Market Pneumonia Virus
#32	SARS-CoV-2 Virus
#33	SARS CoV 2 Virus
#34	SARS-CoV-2 Viruses
#35	COVID-19 Virus
#36	COVID 19 Virus
#37	COVID-19 Viruses
#38	Wuhan Coronavirus
#39	COVID19 Virus
#40	COVID19 Viruses
#41	Severe Acute Respiratory Syndrome Coronavirus 2
#42	{OR #1-#41}
#43	MeSH descriptor: [Acetylcysteine] explode all trees
#44	MeSH descriptor: [Acetylcysteine] explode all trees and with qualifier(s): [pharmacology - PD, therapeutic use - TU]
#45	N-Acetyl-L-cysteine
#46	N Acetyl L cysteine
#47	N-Acetylcysteine
#48	N Acetylcysteine
#49	NAC AL
#50	Acetylcysteine Sodium
#51	Acetylcysteine Zinc
#52	Acetylcysteine
#53	{OR #43-#52}
#54	#42 AND #53

Figure 1. Risk of Bias of each included study

The Risk of Bias in randomized trials tool (ROB-2) tool was used to evaluate to quality of included studies.

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Assimakopoulos et al., 2021						
	Alencar et al., 2021						
	Tasher er al., 2021						
	GayniGaynitdinova et al., 2021						

Domains:

D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement




 High
 Some concerns
 Low

Figure 2. Summary of Risk of Bias. Overall, 50% of the studies are subject to moderate risk of bias while another 25% are subject to serious risk of bias. 50% of studies have some concerns from bias arising from the randomization process, while 25% of them have high risk of the bias. 25% of studies have some concerns from bias due to deviations from intended interventions. 50% of the included studies have some concerns from bias in measurement of the outcome. 50% of the included studies have some concerns from bias in selection of the reported result.

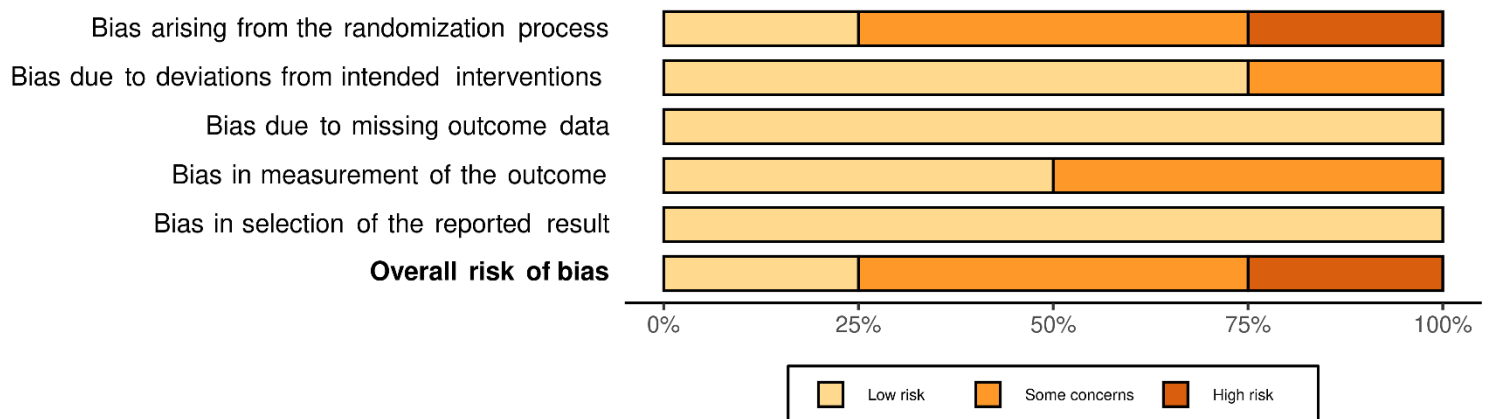


Figure 3. Influence analysis for outcome of intubation rate. After removal of the included study one by one, the result of outcome in interest remain within the confidence interval of primary result and no outlier was identified.

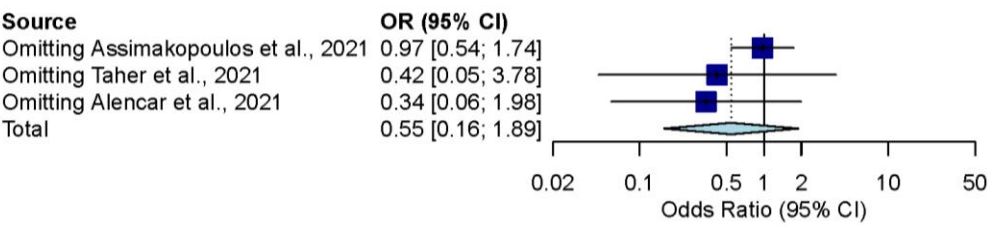


Figure 4. Influence analysis for outcome of improvement of oxygenation index. After removal of the included study one by one, the result of outcome in interest remain within the confidence interval of primary result and no outlier was identified.

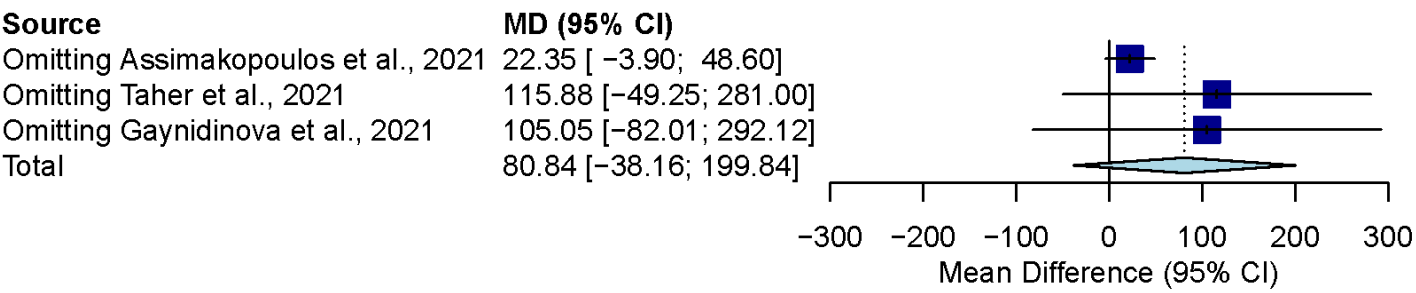


Figure 5. Influence analysis for outcome of duration of hospital stay.

After removal of the included study one by one, the result of outcome in interest remain within the confidence interval of primary result and no outlier was identified.

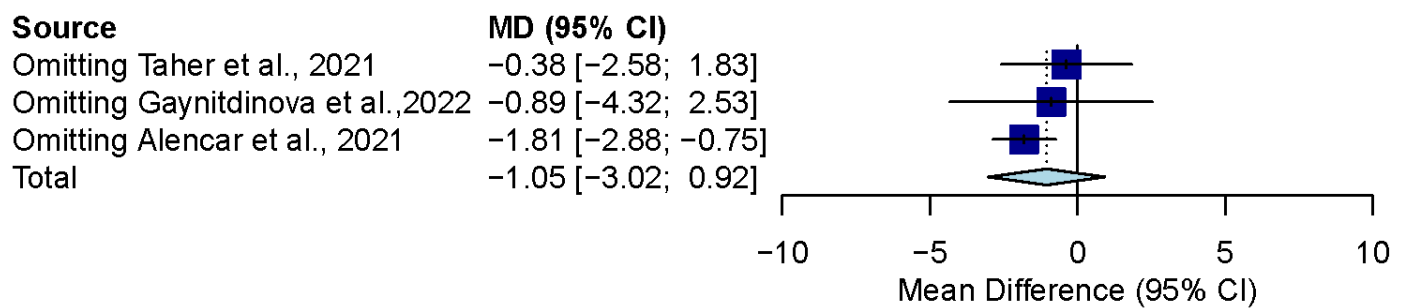


Figure 6. Influence analysis for outcome of mortality. After removal of the included study one by one, the result of outcome in interest remain within the confidence interval of primary result and no outlier was identified.

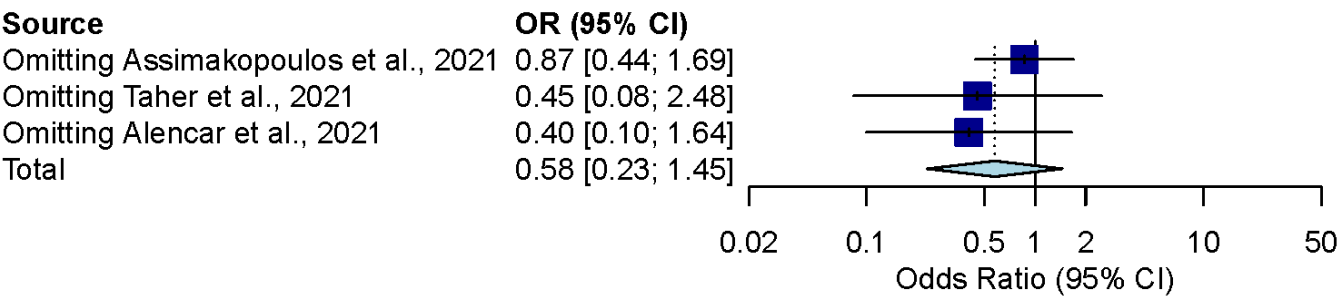


Figure 7. Trial sequential analysis (TSA) for the result of intubation rate.

The cumulative Z-curves did not surpass both the traditional significance boundary and the sequential monitoring boundary. Yet, the z-curve did not reach the RIS and inner wedge of futility, which mean the non-significant result remained inconclusive.

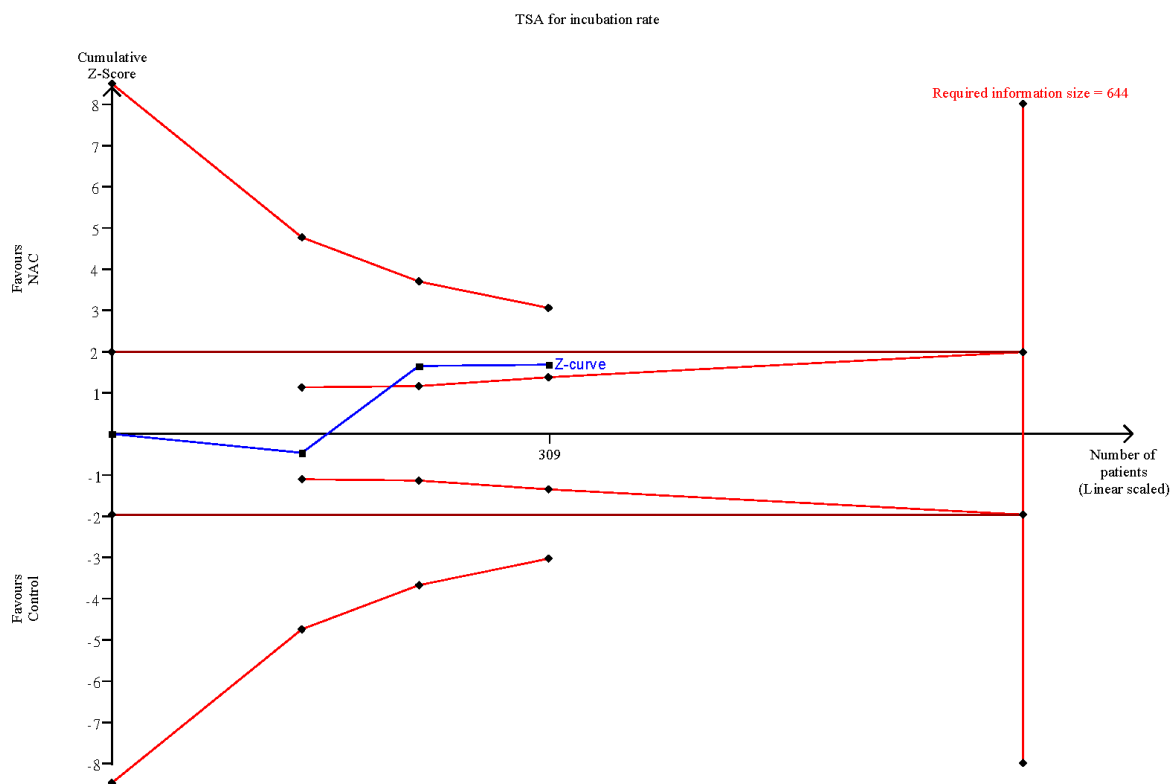


Figure 8. Trial sequential analysis (TSA) for the result of improvement of oxygenation index. The cumulative Z-curves did not surpass both the traditional significance boundary and the sequential monitoring boundary. Yet, the z-curve did not reach the RIS and inner wedge of futility, which mean the non-significant result remained inconclusive.

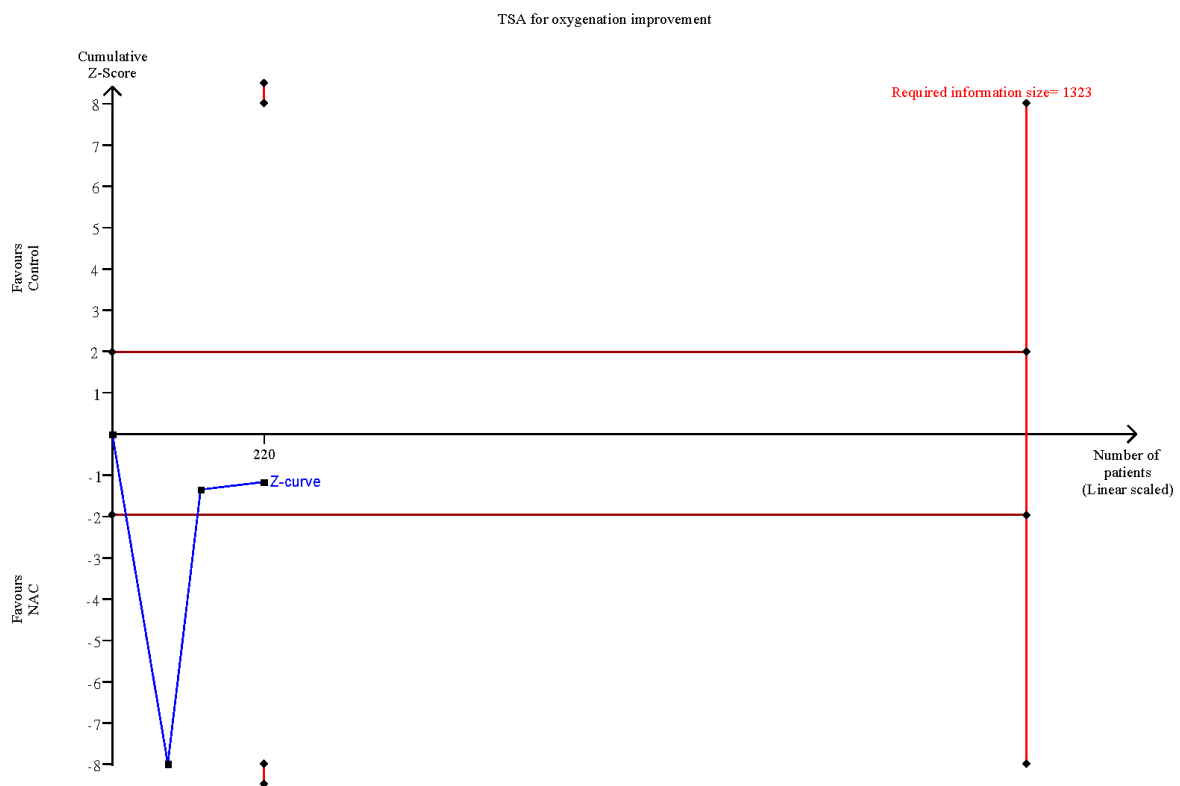


Figure 9. Trial sequential analysis (TSA) for the result of duration of intensive care unit (ICU) stay. Although the cumulative Z-curve does not pass the traditional significance boundary and the sequential monitoring boundary of adjusted confidence interval, it hasn't reached the RIS yet. In other word, the non-significant result between STS group and control group remains inconclusive.

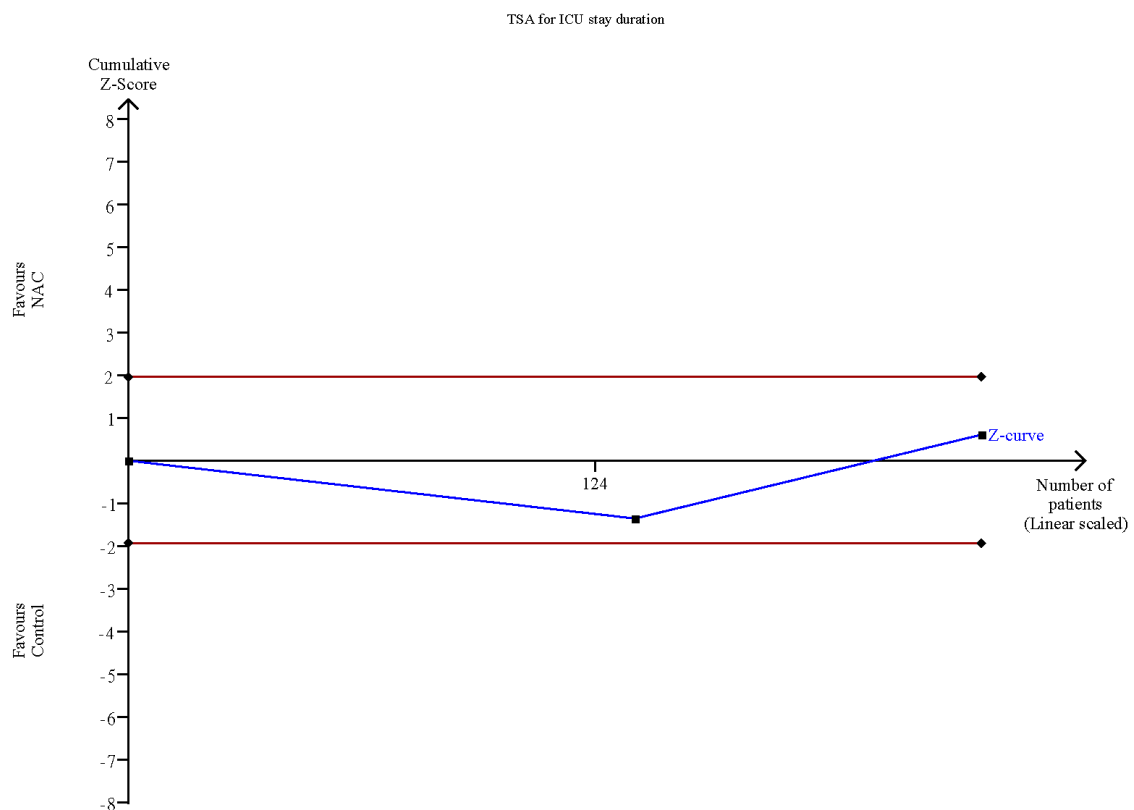


Figure 10. Trial sequential analysis (TSA) for the result of duration of hospital stay. Although the cumulative Z-curve does not pass the traditional significance boundary and the sequential monitoring boundary of adjusted confidence interval, it hasn't reached the RIS yet. In other word, the non-significant result between STS group and control group remains inconclusive.

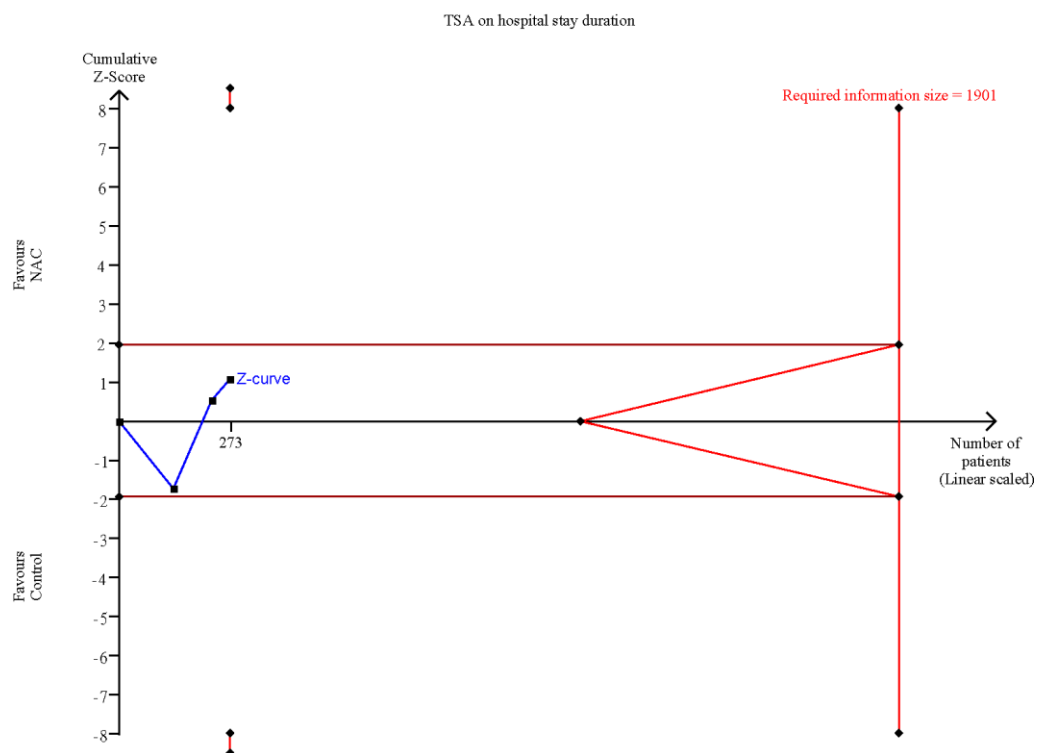


Figure 11. Trial sequential analysis (TSA) for the result of duration of mortality. Although the cumulative Z-curves did not reach the estimated RIS yet, and the cumulative Z-curves has reached in the inner wedge of null result, which indicated the conclusive result of the nonsignificant result.

