

# Supplementary Material

**Humoral immune response to severe acute respiratory syndrome coronavirus-2 vaccination in liver transplant recipients**

## Table of Contents

<b>I. Supplementary Materials and Methods.....</b>	<b>2</b>
Search strategy and results	
Risk of bias	
<b>II. Supplementary Tables.....</b>	<b>8</b>
<b>III. Supplementary Figures.....</b>	<b>11</b>

# I. Supplementary Materials and Methods

## 1. Search strategy and results

### (1) Summary of search results

No.	DB	Results	Duplication
1	PubMed (Medline)	66	
2	EMBASE	267	90
4	Cochrane Library	19	
Number of Search Results (including duplication)		352	
<b>Number of Search Results (without duplication)</b>		<b>262</b>	

### (2) Keywords

PICO	Fields	Keywords	Remarks
<b>P</b>	MeSH	Liver transplantation	<b>A</b>
	TIAB	Liver transplant*	
	TIAB	Liver grafting*	<b>B</b>
	TIAB	Hepatic transplant*	
		<b>A OR B</b>	
<b>I</b>	MeSH	COVID-19 Vaccines	<b>D</b>
	MeSH	SARS-CoV-2	
	MeSH	Covid-19	
	MeSH	Coronavirus	
	MeSH	Ad26COVS1	
	MeSH	2019-nCoV Vaccine mRNA-1273	
	MeSH	BNT162 vaccine	
	MeSH	ChAdOx1 nCoV-19	
	TIAB	COVID-19 vaccin*	<b>E</b>
	TIAB	COVID-19 virus vaccin*	
	TIAB	COVID19 virus vaccin*	
	TIAB	COVID19 vaccin*	
	TIAB	COVID-19 pandemic	
	TIAB	Coronavirus disease-19	

TIAB	SARS-CoV-2
TIAB	SARS2 vaccin*
TIAB	Coronavirus disease 2019
TIAB	Coronavirus disease 19
TIAB	2019-nCoV vaccin*
TIAB	SARS-CoV-2 vaccin*
TIAB	SARS coronavirus 2 vaccin*
TIAB	2019 novel coronavir*
TIAB	2019-nCoV
TIAB	Wuhan coronavir*
TIAB	Severe acute respiratory syndrome coronavirus 2
TIAB	Janssen
TIAB	JNJ-78436735
TIAB	JNJ78436735
TIAB	Johnson and Johnson Covid-19 vaccin*
TIAB	COVID-19 vaccine Johnson and Johnson
TIAB	Moderna
TIAB	2019 nCoV Vaccine mRNA 1273
TIAB	Moderna COVID-19 vaccin*
TIAB	Elasomeran
TIAB	Moderna COVID-19 vaccine RNA
TIAB	COVID-19 vaccine moderna
TIAB	mRNA-1273
TIAB	COVID-19 Vaccine Pfizer-BioNTech
TIAB	BNT 162 vaccin*
TIAB	BNT162 vaccin*
TIAB	Pfizer
TIAB	Pidacmeran
TIAB	Abdavomeran
TIAB	Tozinameran
TIAB	Comirnaty
TIAB	AstraZeneca
TIAB	ChAdOx1 nCoV-19
TIAB	Oxford-AstraZeneca COVID-19 vaccin*
TIAB	ChAdOx1 COVID 19 vaccine*

	TIAB	Covishield	
	TIAB	Vaxzevria	
	TIAB	AZD1222	
	TIAB	AZD-1222	
	TIAB	Coronavir*	
	TIAB	mRNA vaccin*	
	TIAB	ad26.cov2.s vaccine	
	TIAB	Ad26COVS1	
		<b>D OR E</b>	
	MeSH	Immunogenicity, vaccine	
	MeSH	Antibodies	
	MeSH	Antibodies, viral	
	MeSH	Antibody formation	
	TIAB	Seroprevalence*	<b>H</b>
	TIAB	Immunogenicit*	
	TIAB	Vaccine antigenicit*	
	TIAB	Antibod*	
	TIAB	Anti-bod*	
	TIAB	Viral antibod*	
	TIAB	Antibody formation*	
	TIAB	Antibody response*	
	TIAB	Antibody production*	
		<b>C AND F AND I</b>	

### (3) Search strategy

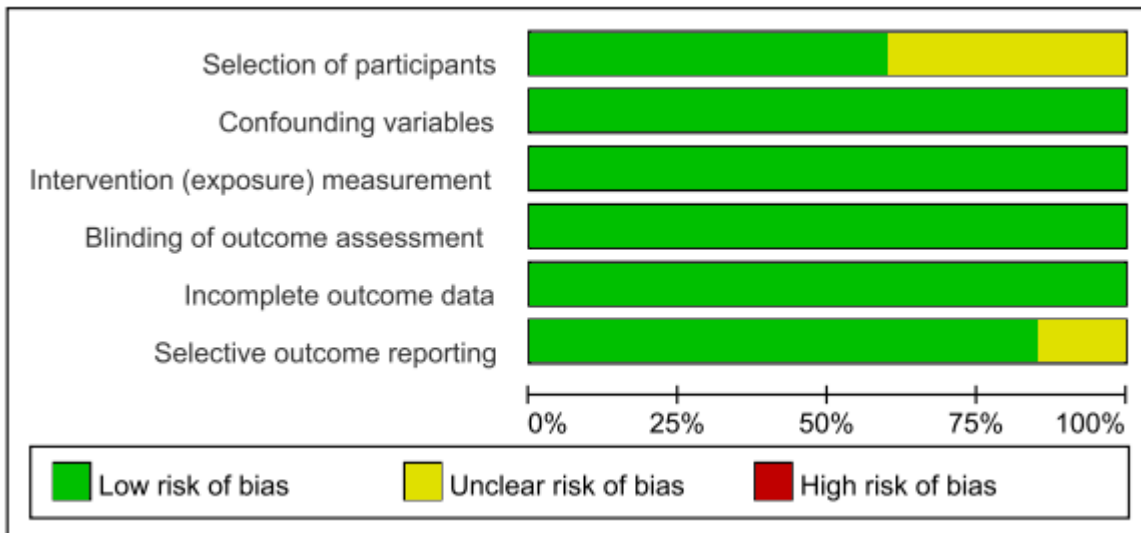
DB	Search Strategy
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<p><b>PubMed</b></p>	<p>("liver transplantation"[MeSH Terms] OR ("liver transplant*"[Title/Abstract] OR "liver grafting*"[Title/Abstract] OR "hepatic transplant*"[Title/Abstract])) AND ("covid 19 vaccines"[MeSH Terms] OR "SARS-CoV-2"[MeSH Terms] OR "covid 19"[MeSH Terms] OR "coronavirus"[MeSH Terms] OR "Ad26COVS1"[MeSH Terms] OR "2019 nCoV Vaccine mRNA 1273"[MeSH Terms] OR "bnt162 vaccine"[MeSH Terms] OR "ChAdOx1 nCoV-19"[MeSH Terms] OR ("covid 19 vaccin*"[Title/Abstract] OR "covid 19 virus vaccin*"[Title/Abstract] OR "covid19 vaccin*"[Title/Abstract] OR "COVID-19 pandemic"[Title/Abstract] OR "coronavirus disease 19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "Coronavirus disease 2019"[Title/Abstract] OR "coronavirus disease 19"[Title/Abstract] OR "2019 ncov vaccin*"[Title/Abstract] OR "sars cov 2 vaccin*"[Title/Abstract] OR "sars coronavirus 2 vaccin*"[Title/Abstract] OR "2019 novel coronavir*"[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR "wuhan coronavir*"[Title/Abstract] OR "Severe acute respiratory syndrome coronavirus 2"[Title/Abstract] OR "Janssen"[Title/Abstract] OR "JNJ-78436735"[Title/Abstract] OR "JNJ78436735"[Title/Abstract] OR "johnson and johnson covid 19 vaccin*"[Title/Abstract] OR "Moderna"[Title/Abstract] OR "2019 nCoV Vaccine mRNA 1273"[Title/Abstract] OR "moderna covid 19 vaccin*"[Title/Abstract] OR "Elasomeran"[Title/Abstract] OR "COVID-19 vaccine moderna"[Title/Abstract] OR "mRNA-1273"[Title/Abstract] OR "COVID-19 vaccine Pfizer-BioNTech"[Title/Abstract] OR "bnt162 vaccin*"[Title/Abstract] OR "Pfizer"[Title/Abstract] OR "Tozinameran"[Title/Abstract] OR "Comirnaty"[Title/Abstract] OR "AstraZeneca"[Title/Abstract] OR "ChAdOx1 nCoV-19"[Title/Abstract] OR "oxford astrazeneca covid 19 vaccin*"[Title/Abstract] OR "chadox1 covid 19 vaccine*"[Title/Abstract] OR "Covishield"[Title/Abstract] OR "Vaxzevria"[Title/Abstract] OR "AZD1222"[Title/Abstract] OR "AZD-1222"[Title/Abstract] OR "coronavir*"[Title/Abstract] OR "mrna vaccin*"[Title/Abstract] OR "ad26.cov2.s vaccine"[Title/Abstract] OR "Ad26COVS1"[Title/Abstract])) AND ("immunogenicity, vaccine"[MeSH Terms] OR "antibodies"[MeSH Terms] OR "antibodies, viral"[MeSH Terms] OR "antibody formation"[MeSH Terms] OR ("seroprevalence*"[Title/Abstract] OR "immunogenicit*"[Title/Abstract] OR "vaccine antigenicit*"[Title/Abstract] OR "antibod*"[Title/Abstract] OR "anti bod*"[Title/Abstract] OR "viral antibod*"[Title/Abstract] OR "antibody formation*"[Title/Abstract] OR "antibody response*"[Title/Abstract] OR "antibody production*"[Title/Abstract]))</p>
<p><b>EMBASE</b></p>	<p>((('liver transplantation'/exp OR 'liver graft'/exp) OR ('liver transplant*':ab,ti OR 'liver graft':ab,ti OR 'hepatic transplant*':ab,ti)) AND (('sars-cov-2 vaccine'/exp OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'coronavirus disease 2019'/exp OR 'coronavirinae'/exp OR 'ad26.cov2.s vaccine'/exp OR 'elasomeran'/exp OR 'bnt 162 vaccine'/exp OR 'vaxzevria'/exp) OR ('covid-19 vaccin*':ab,ti OR 'covid-19 virus vaccin*':ab,ti OR 'covid19 virus vaccin*':ab,ti OR 'covid19 vaccin*':ab,ti OR 'covid-19 pandemic':ab,ti OR 'coronavirus disease-19':ab,ti OR 'sars-cov-2':ab,ti OR 'sars2 vaccin*':ab,ti OR 'coronavirus disease 2019':ab,ti OR 'coronavirus disease 19':ab,ti OR '2019-ncov vaccin*':ab,ti OR 'sars-cov-2 vaccin*':ab,ti OR 'sars coronavirus 2 vaccin*':ab,ti OR '2019 novel coronavir*':ab,ti OR '2019-ncov':ab,ti OR 'wuhan coronavir*':ab,ti OR 'severe acute respiratory syndrome coronavirus 2':ab,ti OR 'janssen':ab,ti OR 'jnj-78436735':ab,ti OR 'jnj78436735':ab,ti OR 'johnson and johnson covid-19 vaccin*':ab,ti OR 'covid-19 vaccine johnson and johnson':ab,ti OR 'moderna':ab,ti OR '2019 ncov vaccine mrna 1273':ab,ti OR 'moderna covid-19 vaccin*':ab,ti OR 'elasomeran':ab,ti OR 'moderna covid-19 vaccine ma':ab,ti OR 'covid-19 vaccine moderna':ab,ti OR 'mrna-1273':ab,ti OR 'covid-19 vaccine pfizer-biontech':ab,ti OR 'bnt 162 vaccin*':ab,ti OR 'bnt162 vaccin*':ab,ti OR 'pfizer':ab,ti OR 'pidacmeran':ab,ti OR 'abdavomeran':ab,ti OR 'tozinameran':ab,ti OR 'comirnaty':ab,ti OR 'astrazeneca':ab,ti OR 'chadox1 ncov-19':ab,ti OR 'oxford-astrazeneca covid-19 vaccin*':ab,ti OR 'chadox1 covid 19 vaccine*':ab,ti OR 'covishield':ab,ti OR 'vaxzevria':ab,ti OR 'azd1222':ab,ti OR 'azd-1222':ab,ti OR 'coronavir*':ab,ti OR 'mrna vaccin*':ab,ti OR 'ad26.cov2.s vaccine':ab,ti OR 'ad26covs1':ab,ti)) AND (('vaccine immunogenicity'/exp OR 'antibody'/exp OR 'virus antibody'/exp OR 'antibody production'/exp OR 'seroprevalence'/exp OR 'immunogenicity'/exp OR (antibodies,antisera AND 'immunoglobulins'/exp)) OR ('seroprevalence*':ab,ti OR 'immunogenicit*':ab,ti OR 'vaccine antigenicit*':ab,ti OR 'antibod*':ab,ti OR 'anti-bod*':ab,ti OR 'viral antibod*':ab,ti OR 'antibody formation*':ab,ti OR 'antibody response*':ab,ti OR 'antibody production*':ab,ti))</p>

**Cochrane**

((MeSH descriptor: [Liver Transplantation] explode all trees) OR (Liver Transplant\*):ti,ab,kw OR (Liver Grafting\*):ti,ab,kw OR (Hepatic Transplant\*):ti,ab,kw) AND ((MeSH descriptor: [COVID-19 Vaccines] explode all trees OR MeSH descriptor: [SARS-CoV-2] explode all trees OR MeSH descriptor: [COVID-19] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR MeSH descriptor: [Ad26COVS1] explode all trees OR MeSH descriptor: [2019-nCoV Vaccine mRNA-1273] explode all trees OR MeSH descriptor: [BNT162 Vaccine] explode all trees OR MeSH descriptor: [ChAdOx1 nCoV-19] explode all trees) OR ((COVID-19 vaccin\*):ti,ab,kw OR (COVID-19 virus vaccin\*):ti,ab,kw OR (COVID19 virus vaccin\*):ti,ab,kw OR (COVID19 vaccin\*):ti,ab,kw OR (COVID-19 pandemic):ti,ab,kw OR (Coronavirus disease-19):ti,ab,kw OR (SARS-CoV-2):ti,ab,kw OR (SARS2 vaccin\*):ti,ab,kw OR (Coronavirus disease 2019 vaccin\*):ti,ab,kw OR (Coronavirus disease 19 vaccin\*):ti,ab,kw OR (2019 nCoV vaccin\*):ti,ab,kw OR (SARS-CoV-2 vaccin\*):ti,ab,kw OR (SARS coronavirus 2 vaccin\*):ti,ab,kw OR (2019 novel coronavirus\*):ti,ab,kw OR (2019 nCoV):ti,ab,kw OR (Wuhan coronavirus\*):ti,ab,kw OR (severe acute respiratory syndrome coronavirus 2):ti,ab,kw OR (Janssen):ti,ab,kw OR (JNJ-78436735):ti,ab,kw OR (JNJ78436735):ti,ab,kw OR (Johnson and Johnson Covid-19 vaccin\*):ti,ab,kw OR (COVID-19 vaccine Johnson and Johnson):ti,ab,kw OR (Moderna):ti,ab,kw OR (2019 nCoV Vaccine mRNA 1273):ti,ab,kw OR (Moderna COVID-19 vaccin\*):ti,ab,kw OR (Elasomeran):ti,ab,kw OR (Moderna COVID-19 vaccine RNA):ti,ab,kw OR (COVID-19 vaccine moderna):ti,ab,kw OR (mRNA-1273):ti,ab,kw OR (COVID-19 Vaccine Pfizer-BioNTech):ti,ab,kw OR (BNT 162 vaccin\*):ti,ab,kw OR (BNT162 vaccin\*):ti,ab,kw OR (Pfizer):ti,ab,kw OR (Pidacmeran):ti,ab,kw OR (Abdavomeran):ti,ab,kw OR (Tozinameran):ti,ab,kw OR (Comirnaty):ti,ab,kw OR (AstraZeneca):ti,ab,kw OR (ChAdOx1 nCoV-19):ti,ab,kw OR (Oxford-AstraZeneca COVID-19 vaccin\*):ti,ab,kw OR (ChAdOx1 COVID 19 vaccine\*):ti,ab,kw OR (Covishield):ti,ab,kw OR (Vaxzevria):ti,ab,kw OR (AZD1222):ti,ab,kw OR (AZD-1222):ti,ab,kw OR (Coronavir\*):ti,ab,kw OR (mRNA vaccin\*):ti,ab,kw OR (ad26.cov2.s vaccine):ti,ab,kw OR (Ad26COVS1):ti,ab,kw)) AND ((MeSH descriptor: [Immunogenicity, Vaccine] explode all trees OR MeSH descriptor: [Antibodies] explode all trees OR MeSH descriptor: [Antibodies, Viral] explode all trees OR MeSH descriptor: [Antibody Formation] explode all trees) OR ((Seroprevalence\*):ti,ab,kw OR (Immunogenicit\*):ti,ab,kw OR (Vaccine antigenicit\*):ti,ab,kw OR (Antibod\*):ti,ab,kw OR (Anti-bod\*):ti,ab,kw OR (Viral antibod\*):ti,ab,kw OR (Antibody formation\*):ti,ab,kw OR (Antibody response\*):ti,ab,kw OR (Antibody production\*):ti,ab,kw)) NOT (MeSH descriptor: [Animals] this term only NOT (MeSH descriptor: [Animals] this term only AND MeSH descriptor: [Humans] this term only))

**2. Risk of bias**



	Selection of participants	Confounding variables	Intervention (exposure) measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Cholankeril 2021	+	+	+	+	+	+
Davidov 2022	+	+	+	+	+	+
D'Offizi 2021	?	+	+	+	+	+
Erol 2021	+	+	+	+	+	+
Fernández-Ruiz 2021	+	+	+	+	+	+
Guarino 2022	+	+	+	+	+	+
Herrera 2021	+	+	+	+	+	+
Huang 2022	?	+	+	+	+	?
Marion 2022	?	+	+	+	+	?
Mulder 2022	?	+	+	+	+	+
Nazaruk 2021	?	+	+	+	+	+
Rabinowich 2021	+	+	+	+	+	+
Rahav 2021	+	+	+	+	+	?
Rashidi-Alavijeh 2021	+	+	+	+	+	+
Ruether 2022	+	+	+	+	+	+
Sakai 2022	?	+	+	+	+	+
Strauss 2021	+	+	+	+	+	+
Thuluvath 2021	+	+	+	+	+	+
Timmermann 2021	?	+	+	+	+	+
Tonitto 2022	?	+	+	+	+	+

## II. Supplementary Tables

**Supplementary Table 1. Summary of the immunogenicity rates of COVID-vaccination in patients with liver transplantation recipients vs. control groups**

Subgroup/Subset	No. of studies	No. of patients, responder/total (LT recipients)	No. of patients, responder/total (controls)	OR (M-H, Random)	95% CI	$I^2$	P for heterogeneity
<b>LT recipients vs. control, overall</b>	16	1049/1592	1318/1602	<b>0.80</b>	<b>0.69 to 0.92</b>	93%	<0.01
<b>LT recipients vs. healthy control</b>	10	750/1078	1008/1029	<b>0.69</b>	<b>0.63 to 0.77</b>	81%	<0.01
<b>LT recipients vs. KT recipients</b>	6	256/443	335/867	<b>1.50</b>	<b>1.35 to 1.67</b>	0%	1.00
LT recipients vs. HT recipients	3	219/368	108/226	1.44	0.89 to 2.32	92%	<0.01
<b>LT recipients vs. liver cirrhosis</b>	2	100/200	109/127	<b>0.54</b>	<b>0.47 to 0.62</b>	0%	0.61

\* CI: confidence interval; M-H: Mantel-Haenszel; No.: number; OR; odds ratio; KT, kidney transplantation; HT, heart transplantation



**Supplementary Table 2. Meta-regression for the immunogenicity rates of COVID-  
vaccination in patients with liver transplantation recipients**

<b>Variable</b>	<b>Coefficient (95% CI)</b>	<b>p-value</b>
Age (year)	-0.001 (-0.023, 0.021)	0.946
Male (%)	0.003 (-0.002, 0.010)	0.184
BMI (kg/m <sup>2</sup> )	-0.067 (-1.349, 0.030)	0.177
Obesity (BMI >30) (%)	-0.005 (-0.020, 0.009)	0.491
Diabetes (%)	0.001 (-0.012, 0.015)	0.197
Hypertension (%)	-0.011 (-0.023, 0.001)	0.062
Chronic kidney disease (%)	-0.006 (-0.012, 0.005)	0.052
Time from LT to vaccination (year)	0.009 (-0.007, 0.026)	0.274
Use of calcineurin inhibitor (%)	-0.002 (-0.006, 0.001)	0.286
Use of MMF (%)	-0.005 (-0.012, 0.002)	0.171
Use of prednisolone (%)	-0.002 (-0.010, 0.004)	0.459
Use of mTOR inhibitor (%)	-0.001 (-0.006, 0.005)	0.846
<b>Immunosuppressant (1 agent) (%)</b>	<b>0.005 (0.001, 0.008)</b>	<b>0.002</b>
Immunosuppressant (2 agent) (%)	-0.003 (-0.007, 0.002)	0.239
Immunosuppressant (3 agent) (%)	-0.005 (-0.019, 0.008)	0.469

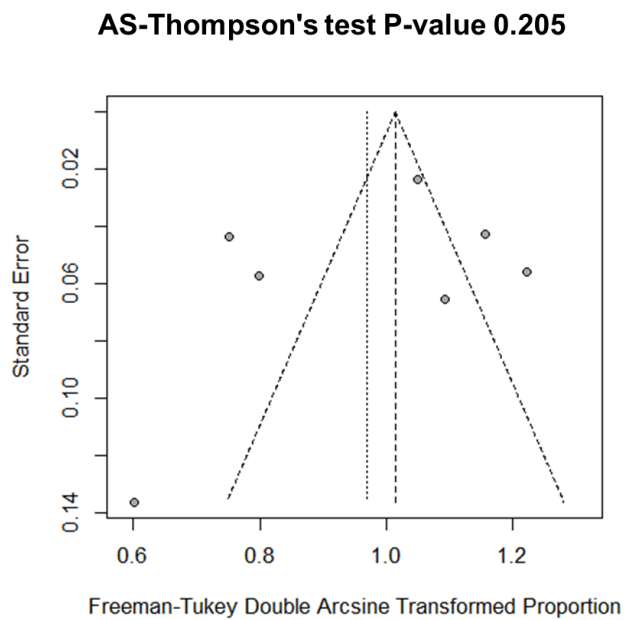
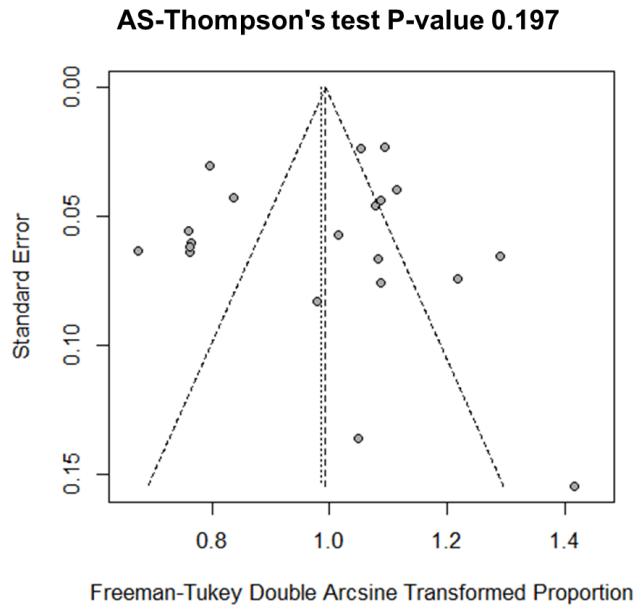
**Supplementary Table 3. Risk factors for the unresponsiveness to vaccination in liver transplantation recipients**

Potential risk factors	No. of studies	Pooled odds ratio	95% CI	$I^2$	P for heterogeneity
<b>Male gender</b>	3	<b>4.40</b>	<b>1.54 to 12.58</b>	0%	0.49
<b>Old age</b>	6	<b>2.82</b>	<b>2.10 to 3.80</b>	0%	0.92
<b>Chronic kidney disease</b>	4	<b>27.56</b>	<b>10.06 to 87.54</b>	95%	<0.01
<b>Obesity</b>	3	<b>2.64</b>	<b>1.14 to 6.09</b>	17%	0.30
<b>Multi-immunosuppressants</b>	6	<b>10.40</b>	<b>6.12 to 17.68</b>	91%	<0.01
<b>High dose steroid</b>	2	<b>5.41</b>	<b>1.66 to 17.67</b>	0%	0.74
<b>High dose MMF</b>	5	<b>5.22</b>	<b>3.66 to 7.45</b>	0%	0.80
High dose tacrolimus	2	2.90	0.92 to 9.09	0%	0.84
<b>Time since liver transplantation</b>	2	<b>4.51</b>	<b>1.46 to 13.97</b>	64%	0.09
<b>Vaccination in 1<sup>st</sup> year of transplantation</b>	3	<b>18.53</b>	<b>7.67 to 44.79</b>	91%	<0.01

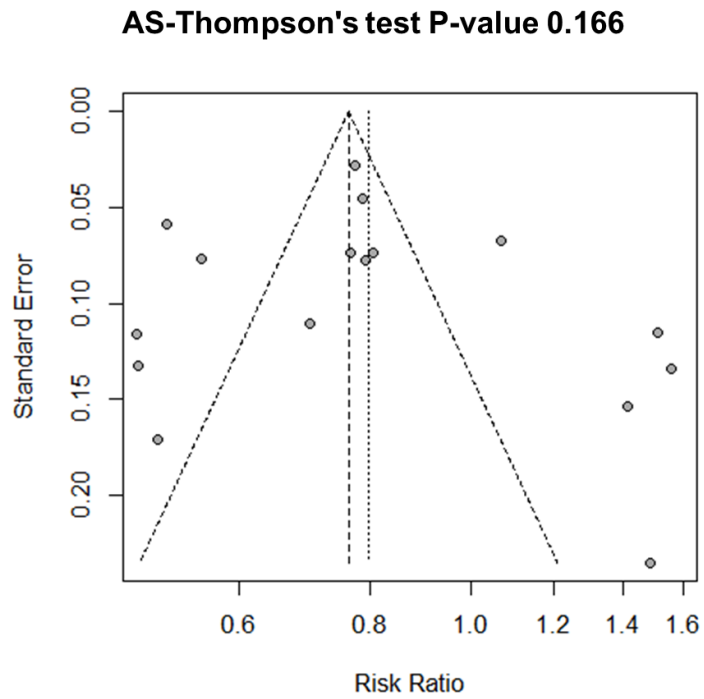
### III. Supplementary Figures

#### Supplementary Figure 1. Funnel plots of immunogenicity rates

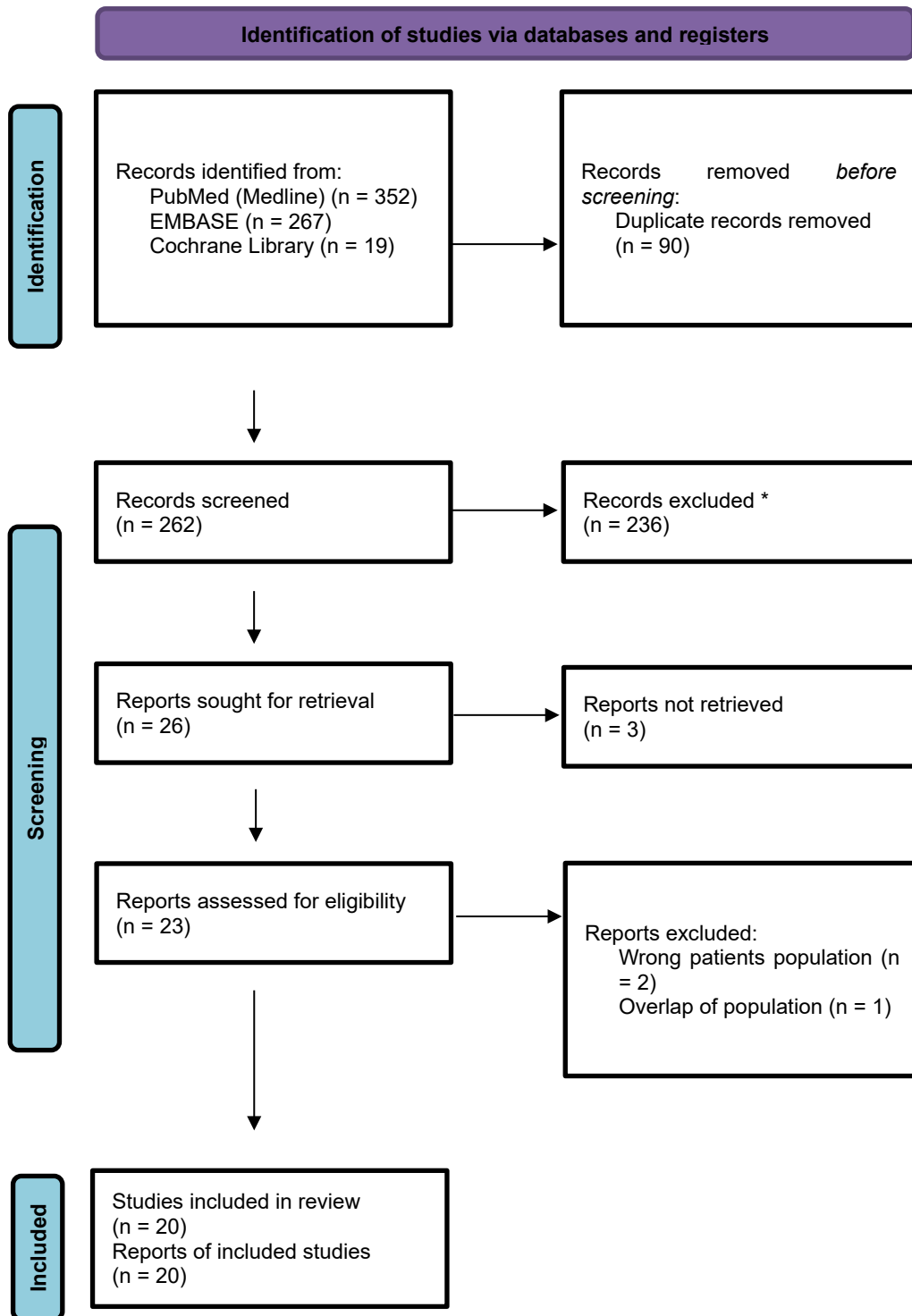
(A) Pooled immunogenicity rate, (B) Comparison of liver transplantation recipients and control groups



**Supplementary Figure 2. Funnel plots of any type of adverse events after the COVID-19 vaccine**



**Supplementary Figure 3. Flowchart of the study inclusion and exclusion process of the systematic review**



\*irrelevant subjects, systematic reviews, case report, abstract only, non-English material

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71