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Review Article

Impact of Hypertension and Cardiovascular Diseases to Immune Response in COVID-19 Vaccination: A Systematic Review

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ABSTRACT

To determine impact of hypertension and cardiovascular diseases towards effectivity and safety of COVID-19 vaccination. Systematic review based on PRISMA statement was done. Searching was conducted in PubMed, ScienceDirect, Scopus, and ProQuest and resulting in 6 studies involving 4,053 participants which deemed on good quality according to Joanna Briggs Institute tools for critical appraisal. After thorough analysis, we found that two out of four studies assessing mRNA-based vaccine found out that hypertension lower antibody response significantly. Two out of two studies assessing inactivated virus vaccine shown that hypertensive patients tend to have lower antibody titers compared to control. One of studies mentioned above found that antibody titer was not different between populations with cardiovascular diseases and control. Hypertension lessened response to COVID-19 vaccination regardless of vaccine type used. However, lack of studies on cardiovascular disease suggested that more studies should be conducted, along with hypertension, in-order to make meta-analysis possible to provide better evidence.

Keywords: antibody; cardiovascular disease; COVID-19; efficacy; hypertension

Highlights: The discovery of the phenomenon of hypertensive patients having lower antibody titers when vaccinated against COVID-19

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic resurging from Wuhan, China. It involve mild to severe respiratory symptoms which could be left fatal at various cases. In order to end its pandemic status, World Health Organization (WHO) has mandated vaccine to be developed and applied. COVID-19 vaccine was first introduced in late 2020 and early 2021, with implementation vaccine begun ever since. In general, COVID-19 vaccine consists of either mRNA or inactivated virus as its base. Recent meta-analysis shown that mRNA-based and inactivated virus COVID-19 vaccines provided efficacy of 94.6% (95% CI 93.6–95. 4) and 80.2% (95% CI 98.0–98.4) respectively.[1] It was also proven safe in pregnancy. A meta-analysis studying mRNA vaccines shown that efficacy rate was 89.5% (95% CI 69.0–96.4) along with low risk of stillbirth and no addition to risk of miscarriage, earlier gestation at birth, pulmonary embolism, placental abruption, and maternal death.[2]

Emergence of newer variants, which known as variants of concern also did not damper its effectivity, with another study shown that fully vaccinated patients shown efficacy of 88.0%, 73.0%, 63.0%, 77.8%, and 55.9% to alpha, beta, gamma, delta, and omicron variants respectively. Boosted patients were more immune to delta and omicron variants with effectivity of 95.5% and 80.8% respectively.[3] Systematic review by Mohammed shown that COVID-19 vaccines deemed to suppress infection rate among population and severity, hospitalization rate, and mortality among COVID-19 patients.[4] A study by Gram found that COVID-19 vaccines successfully reduced hospitalization rates for 14–30 days by 98.1%, 98.1%, and 95.5% for alpha, delta, and omicron variant respectively.[5] Even though several reports have shown that COVID-19 vaccine effectiveness wanes as weeks pass, COVID-19 has been proven to protect population from severity and mortality because of COVID-19 and to improve health and well-being.[5,6]

Response to COVID-19 vaccination was not the same for every recipient, there were several factors playing part. A study in Japan showed that age which older than 60 years, hypertension, high HbA1c (>6.5%), and sedentary lifestyle were significant for inhibiting immune response in COVID-19 vaccination.[7] Other studies mention age, sex, nutritional status, obesity, gut microbiota, polymorphisms, and immune system as determinants.[8] There were several limitations for populations with high blood pressure and cardiovascular disease to take COVID-19 vaccines, even though the limitations have been leniently loosened.[9,10] However, impact of hypertension and cardiovascular diseases to immune response to COVID-19 vaccination is not fully known. Therefore, we conducted a systematic review to determine its relationship to provide better knowledge on COVID-19 vaccination.

MATERIALS AND METHODS

Materials

We conducted systematic review based on The Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA) Statement.[11] Searching was conducted on PubMed, Scopus, ProQuest, and ScienceDirect published in 2022 using specific keywords and medical subheading (MeSH).

Methods

Searching was conducted on PubMed, Scopus, ProQuest, and ScienceDirect using specific keywords and medical subheading (MeSH) terms (Table 1). We applied following inclusion criteria: (1) clinical studies; (2) studying population of people with hypertension and/or cardiovascular disease; (3) studying all sort of COVID-19 vaccine as intervention; (4) studying effectivity as outcome. In addition, we applied following exclusion criteria: (1) co-

existence of other comorbidities; (2) language other than English. Selected studies were appraised using The Joanna Briggs critical appraisal tools.12 Studies were extracted for characteristics and result. Qualitative analysis was conducted to determine the relationship between variables.

Table 1. Keywords Being Used for Searching.

Database	Keywords	Filters
PubMed	("COVID-19 Vaccines"[Mesh]) AND (("Cardiovascular Diseases"[Mesh]) OR "Hypertension"[Mesh])	
Scopus	("COVID-19 vaccine") AND (("hypertension") OR ("cardiovascular disease"))	
ProQuest	("COVID-19 vaccine") AND (("hypertension") OR ("cardiovascular disease"))	"Scholarly Journals", "COVID-19 Vaccines"
ScienceDirect	("COVID-19 vaccine") AND (("hypertension") OR ("cardiovascular disease"))	"Research Articles"

RESULTS AND DISCUSSION

We found total six studies after application of searching strategies and criteria (Figure 1).[13–18] There were three studies across Asia, two across Europe, and one American study involving total 4,053 subjects. There were two studies studying CoronaVac, which is an inactivated virus, and four studies studying BNT162b2 vaccine which is based on mRNA. All studies were eligible to be included in this study after appraisal using Joanna Briggs Institute critical appraisal tools (Table 2). Studies characteristics could be seen in Table 3. All four studies studying mRNA vaccines shown that hypertensive patients tend to have lower antibodies level compared to control, but only two deemed significant.[13–15,17] On the other hand, hypertensive patients which underwent inactivated virus COVID-19 vaccination shown significantly lower antibody level compared to control based on both two studies.[16,18] One of the studies stating that cardiovascular diseases yet to contribute on antibody level. [16] All results could be seen on Table 4.

Table 2. Critical Appraisal Results of Selected Studies.[12]

Studies	Aspect											Overall
	1	2	3	4	5	6	7	8	9	10	11	
Watanabe et al, 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Include
Ebinger et al, 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Delgado et al, 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Soegiarto et al, 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Parthymou et al, 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Rifai et al, 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include

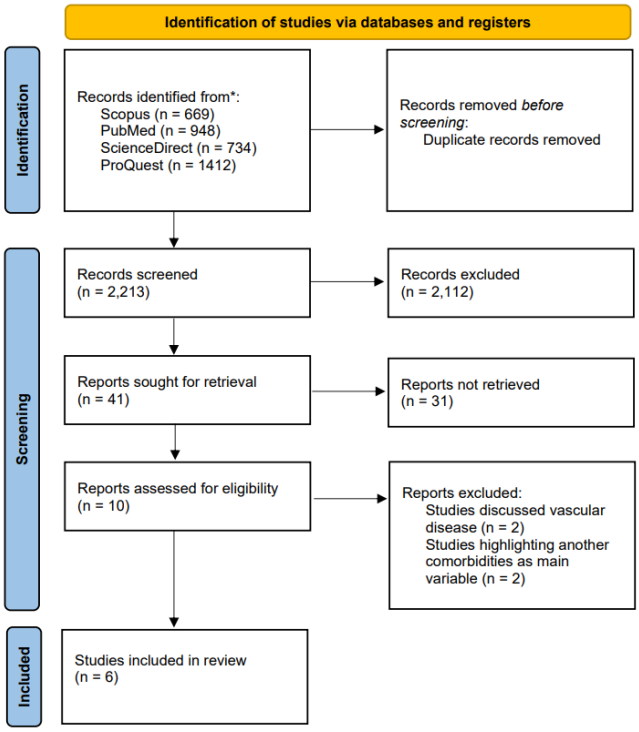

Figure 1. Schematic Workflow of Studies' Finding.[11]

Table 3. Characteristics of Selected Studies

Author	Year	Location	Sample Size	Ab	Vaccine	Dose	Measurement (Weeks after Dose 2)	Age (Years)	Male (%)	BMI (kg/m^2)	Hyper-tension (%)	Dia-betes (%)	Smokers (%)
Watanabe et al[13]	2021	Japan	68	IgS	BNT162b2	2	1-4	29.0 (17.0)	39.5	22.4 (5.5)	15.3	2.4	31.7
Ebinger et al[14]	2022	USA	843	IgS	BNT162b2	2	1, 2, 8, 16, 24, 32, 40	45.0 (13.0)	30.0	-	15.2	-	-
Delgado et al[15]	2022	Spain	2174	IgS	BNT162b2	2	12	45.9	19.9	24.1	8.1	-	22.2
Soegiarto et al[16]	2022	Indonesia	101	IgG	CoronaVac	2	4, 12, 20	47.7 (18.9)	59.5	-	23.7	17.8	10.9
Parthymo u et al[17]	2022	Greece	712	IgS	BNT162b2	2	3, 12	50.8 (11.4)	37.6	26.7 (4.9)	16.2	7.0	34.4
Rifai et al[18]	2022	Indonesia	155	IgG	CoronaVac	2	8, 24	39.0 (9.2)	48.3	27.9 (7.3)	18.7	-	-

Table 4. Results of Selected Studies

Author	Vaccine	Results
Watanabe et al[13]	mRNA	Hypertensive patients presented lower antibody response compared to normotensive (650 ± 1192 vs 1911 ± 1364, p = 0.001). Hypertensive patiens shown significant beta coefficient on univariate and multivariate analysis with -1033.16 (p = 0.005) and -973.27 (p = 0.036) respectively.
Ebinger et al[14]	mRNA	Hypertensive patients shown significant beta coefficient on multivariate analysis with -0.17 and SE of 0.08 (p = 0.041).
Delgado et al[15]	mRNA	Hypertensive patients shown insignificant fold changes with -1.02 (p = 0.8584).
Soegiarto et al[16]	Inactivated	Hypertensive patients shown significant beta coefficient on multivariate analysis with -11.208 (p = 0.038). Patients with history of cardiovascular diseases shown non-significant beta coefficient on multivariate analysis with -10.040 (p = 0.969)
Parthymou et al[17]	mRNA	Hypertensive patients shown insignificant beta coefficient on multivariate analysis with -0.0454 (p = 0.3276).
Rifai et al[18]	Inactivated	Patients with high systolic blood pressure and high diastolic blood pressure shown significant correlation with lower antibody response with R coefficient of -0.172 (p = 0.016) and -0.139 (p = 0.043) respectively second months after vaccination, and R coefficient of -0.284 (p = 0.046) and -0.475 (p = 0.006) respectively six months after vaccination.

Hypertension accounted for lower antibody response in COVID-19 vaccination which was stated in all adjuvant vaccine studies and in most of mRNA vaccine studies. However, some studies showed that there were reports of non-significant differences between groups. Study by Delgado *et al* involving mRNA vaccines reported there were positively increased anti-S protein antibody level after vaccination in patients with older age, more BMI, and arterial hypertension, but exclusive to infected subjects which explained the non-significant of result.[15] However, another mRNA vaccines study by Parthymou *et al* reported that non-significant difference of immune response between hypertensive and non-hypertensive groups was due to confounding factors and differences in size, age, and self-reporting of the populations.[17]

It is known that vaccine response was based on cascades of immune system responses. It depends on the role of T helper 2 (Th2) and B cells to provide a connection to produce long-lived plasma cells which secrete antibodies with high affinity.[19] However, there is differences between mRNA vaccine and adjuvant vaccine in terms of immune response, whereas mRNA vaccine is stimulating cellular immune response and adjuvant vaccine stimulates humoral immune response. Hypertension played role in impairing both of mechanisms. Hypertensive patients had lower Th2 and interleukin 4 (IL-4) levels significantly, thus immune response was impaired.[20] In addition, hypertensive patients developed proinflammatory T cells as a result of high blood pressure which could produce cytokines relating to Th1 and Th17 such as interferon-gamma and interleukin 17A (IL-17A).[21] Another piece of evidence found that angiotensin II, which was over-activated on hypertension, was accounted for the increase in Th1 production and Th2 suppression.[22] Th1 will inhibit humoral immune response, thus inhibiting antibody production.[23] Many other evidences have stated similar hypertension's role in modulating T cell immune metabolism.[24–26] In addition, another study stated that chronic inflammatory due to hypertension will release cytokines due to endothelial dysfunction which included reactive oxidative species (ROS) and interleukins such as IL-1-beta, IL-6, IL-8, IL-17, IL-23, and TNF-alpha. All of these cytokines were responsible for dysfunction of angiotensin II which worsen blood pressure. These cytokines also could alter immune response in hypertension.[27]

Besides applying a damper effect to the immune response of COVID-19 vaccination, hypertension accounted for more severe COVID-19 outcomes.[28–29] Hypertension was found to be the most common comorbidity observed in COVID-19 infection and alongside cardiovascular disease accounted for 2.36 folds higher chance of mortality compared to control.[30] Not only as comorbid, hypertension also played its role as an adverse event towards COVID-19 vaccination. A meta-analysis showed that 3.20% of patients who underwent COVID-19 vaccination showed an abnormal increase in blood pressure, with 0.6% of patients developed hypertensive urgencies and emergencies.[31] This was further confirmed by other studies which stated similar findings.[31–36] Therefore, hypertension provided difficult challenges for healthcare workers who administered COVID-19 vaccine. Not only being impactful to lessen antibody response, but it also accounted for more severe COVID-19 outcomes and more risk towards adverse events. Therefore, hypertension in populations who were prospective for COVID-19 vaccine administration should be taken cautiously and seriously in order to prevent adverse events or severe outcomes. Vaccine developers should be able to make sure that COVID-19 vaccine provided the expected antibody response when given to hypertensive populations in a safe fashion.

Relation between cardiovascular diseases and antibody response is still yet to be known with unclear mechanisms. However, it is

suspected to accounted towards blood circulation and component. Therefore, more studies should be conducted further to determine relation and mechanism of cardiovascular disease impact towards COVID-19 vaccination.

This was a systematic review which provided information on the impact of hypertension and cardiovascular diseases and hypertension towards COVID-19 vaccine response. However, there were limited studies available. In addition, studies included in this review is limited to wide-scope of hypertension which is yet to be graded or classified. This make reviewer could not determine stage which is more responsible for impairment of immune response after vaccination. Therefore, it was recommended that more high-quality studies which involved graded hypertension should be done to make meta-analysis possible to provide a better understanding and knowledge of this field.

STRENGTH AND LIMITATION

The strength of this study was a comprehensive literature search and a bias study was carried out. The limitation of this study is that the amount of literature found is very small.

CONCLUSIONS

Hypertension was linked with lesser antibody response to COVID-19 vaccination in both mRNA-based and inactivated virus-type vaccines. However, cardiovascular diseases are yet to be linked to COVID-19 vaccination response. Due to the few studies which have been retrieved, more studies should be conducted to make a meta-analysis with higher and stronger evidence to be conducted to provide better knowledge on this field.

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This study did not receive any funding.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest.

AUTHOR CONTRIBUTION

Writer, literature searcher, collecting data from literature: KDF. Conceptor and supervision: GS. Review and supervision: LW and DP.

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