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Covid-19 and its Correlation with Thromboembolic and Cardiovascular Events: a Systematic Review

Covid-19 e sua Correlação com Eventos Tromboembólicos e Cardiovasculares: uma Revisão Sistemática

Carolina Santos Mota*[a]; Ana Paula Silva de Jesus[a]; Isis Nunes Veiga[abc]

[a]Centro Universitário Dom Pedro II. BA, Brazil.
[b]Universidade Católica de Salvador, Stricto Sensu Graduate Program in Family in Contemporary Society. BA, Brazil;
[c]Centro Universitário Unifas - Unime. BA,
*E-mail: carolinamota097@gmail.com

Abstract

Identified in China in December 2019 as a new class of viral pneumonia of unknown origin, the new Coronavirus has already passed the milestone of 100 million people infected worldwide. The clinical course of this infection is characterized by fever, cough, upper airway congestion and complications related to Acute Respiratory Distress Syndrome. In addition, the virus can have repercussions that go beyond the impairment of the respiratory system, affecting other systems. Therefore, the aim of this study is to describe the correlation between Covid-19 and thromboembolic and cardiovascular events. It is a Systematic Review that was submitted to searches in the PubMed, SciELO, Lilacs and Bireme databases. Six observational studies comprising 1539 patients were included in this review. The quality of the articles was evaluated according to the New Castle-Ottawa scale. After extracting data from the studies, it was observed that hospitalized patients diagnosed with Covid-19 infection are more likely to develop Venous Thromboembolism (VTE) and Pulmonary Embolism (PE), as well as cardiovascular events, although the latter are less frequent. These patients also have alterations in the pulmonary parenchyma, being proportional to the severity of the case, as well as the prevalence of d-dimer, the rate of thrombosis in the pulmonary artery, the need for intensive care and the mortality rate. Thus, the severe form of infection by Covid-19 manifests consequences that do not only involve the respiratory system, compromising the blood clotting of affected patients, leading to a higher incidence of thromboembolic and cardiovascular events.

Keywords: Cardiovascular Diseases. Thrombosis. Coronavirus Infections.

Resumo

Identificado na China em dezembro de 2019 como uma nova classe de pneumonia viral, de origem desconhecida, o novo Coronavírus já ultrapassou o marco de 100 milhões de pessoas infectadas em todo o mundo. A evolução clínica desta infecção é caracterizada por febre, tosse, congestão das vias aéreas superiores e complicações relacionadas a um quadro de Síndrome do Desconforto Respiratório Agudo. Além disso, o vírus pode apresentar repercussões que vão além do comprometimento do sistema respiratório, afetando outros sistemas. Portanto, o objetivo deste estudo é descrever a correlação entre a Covid-19 e os eventos tromboembólicos e cardiovasculares. Trata-se de uma Revisão Sistemática que foi submetida a pesquisas nos bancos de dados PubMed, SciELO, Lilacs e Bireme. Foram incluídos 6 estudos observacionais envolvendo 1539 pacientes nesta revisão. A qualidade dos artigos foi avaliada de acordo com a escala New Castle-Ottawa. Após a extração de dados dos estudos, observou-se que pacientes hospitalizados e diagnosticados com infecção por Covid-19 apresentam maior predisposição a desenvolver Tromboembolismo Venoso (TEV) e Embolia Pulmonar (EP), bem como eventos cardiovasculares, apesar destes últimos serem menos frequentes. Estes pacientes também cursam com alterações do parênquima pulmonar sendo proporcionais a gravidade do caso, assim como a prevalência de d-dímero, a taxa de trombose na artéria pulmonar, a necessidade de cuidados intensivos e a taxa de mortalidade. Assim, a forma grave da infecção por Covid-19 manifesta consequências que não envolvem apenas o sistema respiratório, comprometendo a coagulação sanguínea dos pacientes acometidos levando a maior incidência de eventos tromboembólicos e cardiovasculares.

Palavras-chave: *Doenças Cardiovasculares. Trombose. Infecções por Coronavírus.*

1 Introduction

Identified in China in December 2019 as a new class of viral pneumonia of unknown origin, the new Coronavirus, later recognized and notified by the World Health Organization (WHO) has already passed the milestone of 100 million people infected worldwide, accounted until February of 2021. [1-3].

The clinical course of this infection is characterized by fever, cough, upper airway congestion and complications related to clinical sign of Acute Respiratory Distress Syndrome (ARDS). In addition, the virus may have repercussions that go beyond respiratory system impairment, affecting other systems and, in this way, the patient has a high probability of admission to the Intensive Care Unit (ICU), which may result in death[1-6].

In cases of death, the mortality rate of positive individuals varies between the profile of affected patients, and it was reported in previous studies that this marker in patients with cardiovascular comorbidities was up to 3.15 times higher than those without preexisting cardiovascular diseases. In addition, among the patients admitted into the hospital, the literature indicates that approximately from 17.1% to 59.6% present comorbidities in the cardiovascular system, indicating that this condition is correlated with the infection severity[7].

Initially, the evidence on the effects of COVID-19 on the cardiovascular system was little described, however, studies point out that respiratory infections play an important role in the incidence of acute myocardial infarction (AMI) and ischemic stroke (AVEi). Therefore, as the deaths caused by coronavirus increase, the impact of the virus on the cardiovascular system becomes increasingly studied.[8,9]

In addition, previous studies also report the occurrence of changes in blood clotting of patients infected with the virus. Although the exact origin of the association between high D-dimer values (marker of thrombin generation and fibrinolysis) and worse outcomes, is still not completely clarified, the relationship among this marker, deep venous thrombosis (DVT) and pulmonary embolism (PE), follows under investigation[10].

In view of the continuing expansion of the pandemic, a thorough understanding of the interaction between these systems and the infection by coronavirus is needed[7]. With a view to addressing this issue, the present review aims to describe the correlation between COVID-19 and thromboembolic and cardiovascular events.

2 Development

2.1 Methodology

This systematic Review was submitted to research in the online databases Pubmed, SciELO, Lilacs and Bireme, using the search keywords defined according to the PECO strategy (P= Adult, E= COVID-19, C= Control Group, O= Cardiovascular System). In the Medical subject headings (MeSH) for searches performed in PubMed and for searches performed in the other databases, the descriptors in Health Sciences (DeCS) were used. The research procedure occurred according to the recommendation of the main items to report systematic reviews and Meta-analyzes – PRISMA[11].

The observational studies published in 2020, in which patients >18 years of age of both genders, who were hospitalized , diagnosed with SARS-COV-2 infection confirmed by PCR, presented some thromboembolic or cardiovascular events during hospitalization, were defined as inclusion criteria. On the other hand, studies involving the pediatric and neonatal population and patients infected with other respiratory viruses were defined as exclusion criteria.

From these criteria, the following combinations of descriptors were defined: "cardiac involvement" e "cardiovascular diseases" and "thrombosis" and "coronavirus infections" according to the DeCS and (("Coronavirus infection") AND "Cardiovascular diseases") AND "Thrombosis" according to MeSH. Data were collected from December 2020 to March 2021, from the reading of titles and abstracts, when the first exclusion occurred and, from the reading of the studies in full, when the second exclusion was made.

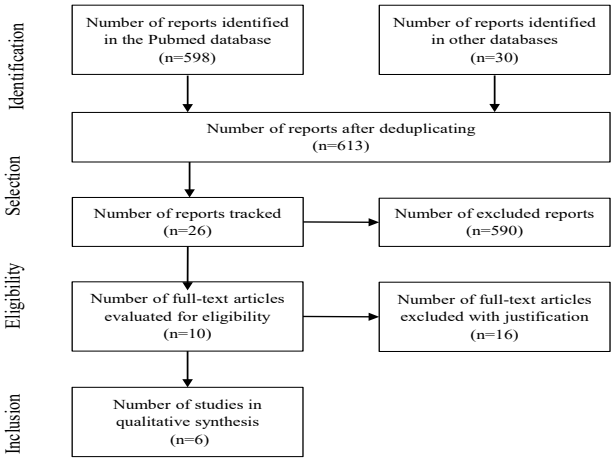
The evaluation of the methodological quality in relation to the risk of bias of cohort studies was carried out through the Newcastle-Ottawa scale. On this scale, the measurement was calculated in three components: selection of the groups, ranging from zero to four points; comparability, from zero to two points and exposure/result, from zero to three points.

The data reported in this review were collected based on the identification of the objective described in each study and its methodological particularities, namely: sample size, evaluation instruments, evaluated variables and results obtained.

The data were presented in tables with exposure of the values and confidence interval or "p" value of significance, being considered by the studies as significance when $p<0.05$. The discussion was elaborated based on the results by evaluated outcome.

Below is a flowchart of the studies identified and subsequently selected for this Systematic Review.

Figure 1 - Flowchart of the selection of articles indexed in PubMed and other databases (Lilacs and SciELO)



Source: The authors.

The Newcastle-Ottawa scale was used to evaluate the included studies, and the definition of the items analyzed was numerically represented, considering each asterisk (*) equivalent to one point, totaling from zero to nine points (Table 1).

Table 1 - Quality assessment of selected articles according to the Newcastle-Ottawa scale

Author	Type of Studies	Evaluated Items			Total
		Selection	Compara-bility	Exposure	
Contou et al.[12]	Cohort	4*	1*	3*	8
Kampouri et al.[13]	Cohort	3*	1*	3*	7
Klok et al.[14]	Cohort	2*	-	2*	4
Londigiani et al.[15]	Cohort	3*	-	2*	5
Mueller-Peltzer et al.[10]	Cohort	3*	1*	3*	7
Rothstein et al.[16]	Cohort	3*	-	3*	6

Source: Research data.

Table 2 - Results found after extracting data from the included articles

Author	Methodology		Main findings
Contou et al.[12]	**Type of Study:** Cohort **Sample:** 92 adult patients, aged between 55 and 70 years, of both sexes. 26 patients, of the 92 included in the study, underwent CTPA and were analyzed in 2 groups: **G1:** 16 patients with COVID-19, ARDS and PE; **G2:** 10 COVID-19 and ARDS patients.	**Analyzed variables:** Prevalence of uni and bilateral PE; ICU mortality rate.	17% (16) of the patients had PE, of these, 19% (3 patients) were bilateral and 81% (13 patients) were unilateral. ICU mortality was higher in G1 compared to G2 (p=0.04).
Kampouri et al.[13]	**Type of Study:** Retrospective cohort **Sample:** 443 adult patients, aged between 59 and 69 years of both sexes, were analyzed and it was observed that at least one thromboembolic event occurred in 41 of these patients, being the same divided into groups: **G1:** 14 patients who presented VTE at hospital admission. **G2:** 27 patients who had VTE during hospitalization (infection considered after 5 days of hospital stay). **G3:** Patients who did not have VTE.	**Evaluated variables:** Rate of VTE (including: PE or thrombosis at other sites). Intensive care needed. Prevalence of D-dimer.	The VTE rate among the patients included in this study was 9.3%. As for G1: 3 patients were admitted directly to the ICU and 11 to the wards. Regarding G2: 9 patients were admitted into hospital in wards and 18 in ICU. In both groups (G1 and G2), those who were hospitalized in the ICU showed higher rates of VTE (22.3%). D-dimer values showed a significant difference among the G3 patients when compared to G1 and G2 (p=0.001).
Klok et al.[14]	**Type of Study:** Cohort. **Sample:** 184 patients, of both sexes, with a mean age of 64 years.	**Analyzed variables:** Incidence of: PE, VTE, AVEi, AMI and arterial embolism.	It was observed that 31% of the patients developed thrombotic complications, namely: PE, VTE and arterial embolism. It was not identified among the evaluated patients: stroke and AMI.
Lodigiani et al.[15]	**Type of Study:** Retrospective cohort **Sample:** 388 symptomatic adult patients, aged between 55 and 85 years, of both sexes.	**Analyzed variables:** TEV and PE rate. Rate of cardiovascular events, which included Acute Coronary Syndrome, AMI, and ischemic stroke. Length of stay in the hospital unit.	**Main findings:** 4.4% of patients had VTE, among these, 63% were associated with PE and 50% associated with VTE. Cardiovascular events were observed in 3.3% of patients (9 patients had stroke and 4 patients had coronary syndrome and AMI). It was observed that 15.7% of the patients were referred to the ICU and stayed for about 12 days, while the others remained in general ward around 4 days.
Mueller-Peltzer et al.[10]	**Type of Study:** Retrospective cohort. **Sample:** 16 patients, aged between 47 and 77 years, of both sexes. All the patients were on MV and 5 of them received ECMO.	**Evaluated variables:** Pulmonary artery thrombosis rate. Prevalence of D-dimer. Changes in lung parenchyma (detected by CT angiography).	**Main findings:** 56% of patients had pulmonary artery thrombosis. There was a significant association of pulmonary artery thrombosis with more severe parenchymal changes (p=0.006). There was a trend towards higher levels of d-dimer in patients with pulmonary artery thrombosis, but without statistical significance (p=0.08)
Rothstein et al.[6]	**Type of Study:** Retrospective cohort **Sample:** 884 patients, adult, of both sexes, aged between 18 and 59 years.	**Analyzed variables:** AVEi and HIC rate.	**Main findings:** 2.4% of the patients had ischemic stroke, while 0.9% had ICH.

PTC: pulmonary Angio tomography, PE: Pulmonary Embolism, ARDS: Acute respiratory distress syndrome, G1: group 1, G2: group 2, VTE: venous thromboembolism, AVEi: ischemic stroke, G3: group 3, ischemic stroke, AMI: acute myocardial infarction myocardium, ECMO: extracorporeal membrane oxygenation, ICH: intracranial hemorrhage.
Source: Research data.

2.2 Description of the Selected Studies

In the studies selected to make up this review, the patients were classified in different ways, where only adult, hospitalized, diagnosed with COVID-19, confirmed by PCR, and who presented some thromboembolic or cardiovascular event during the hospitalization period, were evaluated. The

studies of Countou et al.[12] and Kampouri et al.[13] categorized the patients into groups, comparing the study group with control groups with similar health condition. And the studies of Klok et al.[14], Lodigiani et al.[15], Mueller-Peltzer et al.[10] and Rothstein et al.[16] did not delimit groups for the analysis.

The following outcomes were analyzed: Rate of VTE and PE, cardiovascular events (including acute coronary syndrome, AMI, AVEi and HIC), need for intensive care, changes in the pulmonary parenchyma, prevalence of d-dimer, rate of thrombosis in the pulmonary artery and mortality rate.

2.3 Rate of Venous Thromboembolism and Pulmonary Embolism

Regarding the TEV and PE rate, Contou et al.[12] identified in their cohort that 17% of the patients evaluated developed PE. Whereas Kampori et al.[13] observed that of the 9.3% of the patients who presented VTE in their study, 34% of them were verified at hospital admission and the others during hospitalization. In addition, they pointed out that in both groups observed in their study, patients who needed intensive care developed higher rates of VTE.

In the study by Klok et al.[14] the total of 31% of the patients included treated with PE, VTE and arterial embolism, and the PE was the most frequent event. As well as in the study by Lodigiani et al.[15] in which 4.4% of the patients studied presented thromboembolic complications, 63% of them developed PE and 50% VTE.

The results found in the above mentioned studies are in accordance with the data previously exposed in the literature, in which the possible relation of COVID-19 with coagulopathy events is described, especially demonstrated in critical infected patients, associating the elevation in the incidence of PE and pulmonary thrombosis. In addition, there are reports of other risk factors linked to the development of VTE in these patients, such as the long hospital stay, which may be significant in severe cases[17].

2.4 Cardiovascular Events

Regarding the cardiovascular events, the study carried out by Klok et al.[14] that also presented the objective of identifying the rate of AVEi and AMI, did not show any case. The authors report that this can be justified by the short period of observation of patients (7 days). On the other hand, Lodigiani et al.[15] revealed in their study that 13 of the 388 patients evaluated had cardiovascular events, of whom 9 developed AVEi and 4 patients acute coronary syndrome. Whereas Rothstein et al.[16] also revealed in their cohort that 20 (equivalent to 2.4%) patients had AVEi and 8 (0.9%) had HIC.

Rothstein et al.[16] report that the HIC rate found in their study is relatively high and worrisome, since the use of anticoagulant therapy in infected patients has been increasing. The authors point out that there are significant limitations in the studies regarding the sample base of patients with cerebrovascular events and that greater observational studies are needed, including patients with COVID-19 and cerebrovascular events, for a more accurate determination of the risk factors of these events[16].

2.5 Prevalence of D-dimer

Regarding the prevalence of D-dimer, Kampouri et al.[13] reported that there was a statistically significant difference in the values of this variable when comparing the patients who presented VTE at hospital admission or during hospitalization with those who did not present VTE. In contrast, Mueller-Peltzer et al.[10] identified a tendency to higher values in patients who had thrombosis in the pulmonary artery, but without statistical relevance.

Changes in blood clotting have already been described in patients infected with COVID-19 and elevated D-dimer values can be recognized as a predictor of mortality. In this infection, as in others, there is a generation of a diffuse inflammatory state and one of the main laboratory responses is the increase in D-dimer values, being directly proportional to the severity of the clinical sign[17].

2.6 Rate of Pulmonary Artery Thrombosis

Regarding the rate of thrombosis in the pulmonary artery, Mueller-Peltzer et al.[10] identified it in 56% of the patients studied. In this cohort, the authors emphasize that this rate may be influenced by the referral of the most severe patients to ECMO. ECMO is a therapeutic modality that allows temporary support of pulmonary and/or cardiac function. In this study, ECMO was used in the venous configuration (VV-ECMO), which is the modality of choice in cases of respiratory failure with preserved cardiac function[10].

2.7 Intensive Cares

Regarding the intensive cares, in the study carried out by Kampouri et al.[13] 51% of the patients who developed thrombotic events after the infection with the coronavirus needed hospitalization in the ICU, while in the study by Lodigiani et al.[15] only 15.7% of the patients analyzed developed the severe form of the disease and were sent to ICU.

The data found in the above studies coincide with the results obtained in a cohort study carried out in Brazil, where the authors report that although the rates may vary, it is estimated that up to 25% of patients hospitalized for COVID-19 need intensive care. This index varies according to cultural differences related to ICU admission criteria and regional individuals, such as the population age group and the prevalence of other comorbidities. Similarly, ICU mortality rates vary from 22% to 67%[18].

2.8 Mortality Rate

Regarding the mortality rate, Contou et al.[12] described that this indicator in the ICU was higher in patients who had PE compared to those who did not develop it. This result corroborates the data already described in previous studies,

in which they classify PE as one of the cardiovascular complications that most cause death in the hospital after AMI and AVEi[19].

2.9 Changes in the Pulmonary Parenchyma

Among the studies included in this review, only the cohort performed by Mueller-Peltzer et al.[10] analyzed the outcome of changes in the pulmonary parenchyma and was reported as a result, which showed a significant association of pulmonary artery thrombosis with more severe parenchyma changes.

3 Conclusion

Through the results of the studies analyzed, it is observed that patients infected with SARS-COV-2 seem to have a higher predisposition to develop VTE and PE, as well as other cardiovascular events, although these are less frequent. These patients also have alterations in the pulmonary parenchyma, being proportional to the severity of the case, as well as the prevalence of d-dimer, the rate of thrombosis in the pulmonary, the need of intensive cares and the mortality rate.

Considering that the pandemic continues to expand and that infection by COVID-19 manifests consequences that go beyond the respiratory system impairment, it is of great importance to carry out new observational studies that assess possible risk factors for thromboembolic and cardiovascular events and contribute to their prevention.

References

1. Oliveira JS, Veiga IN, Mota CS. Intervenção fisioterapêutica em uma criança com coronavírus em um hospital de referência: relato de caso. Rev Pesq Fisioter 2021;11(1):1-6. doi: 10.17267/2238-2704rpf.v11i1.3380

2. Awadasseid A, Wu Y, Tanaka Y, Zhang W. Initial success in the identification and management of the coronavirus disease 2019 (COVID-19) indicates human-to-human transmission in Wuhan, China. Int J Biol Sci 2020;16(11):1846-60. doi: 10.7150/ijbs.45018

3. WHO - World Health Organization. Coronavirus Disease (COVID-19) Dashboard [Internet]. 2021.[citado 2021 fev. 20]. Disponível em: https://covid19.who.int/

4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(1):497-506. doi: 10.1016/S0140-6736(20)30183-5

5. Silva CMS, Andadre NA, Nepomuceno B, Xavier DS, Lima E, Gonzalez I, et al. Evidências científicas sobre Fisioterapia e funcionalidade em pacientes com COVID-19 Adulto e Pediátrico. J Hum Growth Dev 2020;30(1):148-55. doi: 10.7322/jhgd.v30.10086

6. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. JAMA Cardiol 2020;5(7):831-40. doi:10.7322/jhgd.v30.10086

7. Martins JDN, Sardinha DM, Silva RR, Lima KVB, Lima LNGC. As implicações da COVID-19 no sistema cardiovascular: prognóstico e intercorrências. J Health Biol Sci 2020;8(1):1-9. doi: 0.12662/2317-3206jhbs.v8i1.3355.

8. Ferrari F. COVID-19: Dados atualizados e sua Relação Com o Sistema Cardiovascular. Arq Bras Cardiol 2020; 114(5):823-826. doi: 10.36660/abc.20200215

9. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol2020;5(7):819-24.doi:10.1001/jamacardio.2020.1096 Mueller-Peltzer K, Krauss T, Benndorf M, Lang CN, Bamberg F, Bode C et al. Pulmonary artery thrombi are co-located with opacifications in SARS-CoV2 induced ARDS. Respiratory Med 2020;172:106135. doi: 10.1016 / j.rmed.2020.106135.

10. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. PLoSMed 2009;6(7):e1000097.

11. Contou D, Pajot O, Cally R, Logre E, Fraissé M, Mentec H, et al. Pulmonary embolismo r thrombosis in ARDS COVID-19 patients: A French monocenter retrospective study. PLOS ONE. 2020;15(8). doi: https://doi.org/10.1371/journal.pone.0238413.

12. Kampouri E, Filippis P, Viala B, Mean M, Pantet O, Desgranges F, et al. Predicting Venous Thromboembolic Events in Patients with Coronavirus Disease 2019 Requiring Hospitalization: an Observational Retrospective Study by the COVIDIC Iniatiative in a Swiss University Hospital. BioMed Res Int 202. doi: doi.org/10.1155/2020/9126148

13. Klok FA, Kruip MJHA, Van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-7. doi: 10.1016 / j.thromres.2020.04.013

14. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9-14. doi: 10.1016/j.thromres.2020.04.024.

15. Rothstein A, Oldridge O, Schwennesen H, Do D, Cucchiara BL. Acute Cerebrovascular Events in Hospitalized COVID-19 Patients. Stroke 2020;51(9):e219-e222. doi: https://doi.org/10.1161/STROKEAHA.120.030995

16. Carvalho ACS, Barros LSA, Tenório ECPT, Lopes TP, Lopes LP, Cruz CM. Moduladores de coagulação alterados comprometem os pacientes infectados com COVID-19. Braz J Health Rev 2020;3(5):11624-44. doi: https://doi.org/10.34119/bjhrv3n5-021

17. Nascimento JPN, Costa RL, Simvoulidis LFN, Pinho JC, Pereira RS, Porto AD et al. COVID-19 e Injúria Miocárdica em UTI Brasileira: Alta Incidência e Maior Risco de Mortalidade Intra-Hospitalar. Arq Bras Cardiol 2021;116(2):275-82. doi: https://doi.org/10.36660/abc.20200671

18. Silva JP, Souza RB, Oliveira LC, Rocha LB, Spinelli JLM, Couto MHSHF. Perfil Epidemiológico do Tromboembolismo Pulmonar no Brasil de 2015 a 2019. BEPA, Bol. Epidemiol Paul 2021;18(208).