ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com
ISSN NO. 2320-5407

REVIEWER'S REPORT

Date:5/11/2025

Manuscript No.: **IJAR-54645**

Title: Cerebral Vasoreactivity to Carbon Dioxide Assessed by Transcranial Doppler Ultrasound in PostÂ–COVID-19 Patients: A Moroccan Comparative Study

Recommendation.

Accept After Minor Revision

Rating	Excel.	Good	Fair	Poor
Originality	✓			
Techn. Quality	✓			
Clarity	✓			
Significance	✓			

Reviewer Name:Mrs. Shreya Vaz

Reviewer's Comment forPublication.

Detailed Reviewer'sReport

This article is based comprises a brief contents.

This prospective, observational case-control study examines cerebrovascular reactivity (CVR) to carbon dioxide in 50 patients who recovered from moderate or severe COVID-19, compared to 25 non-COVID-19 controls. The research demonstrates that post-COVID-19 patients exhibit **significantly impaired cerebral vasoreactivity**, as evidenced by reduced cerebrovascular reactivity indices and breath-holding index (BHI) values, suggesting persistent endothelial dysfunction despite clinical recovery. The study has merit in highlighting an Important post-COVID sequela with potential clinical implications for perioperative and critical care management, though methodological limitations warrant cautious interpretation.

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

Strengths of the Study

Research Design and Methodology

The study employs a well-structured prospective design conducted over a defined period (September 2021 – June 2022) at a military hospital in Morocco. The use of a single, experienced operator for all transcranial Doppler (TCD) measurements strengthens internal consistency and minimizes operator variability. The standardized protocol—including a minimum 30-second baseline recording requirement, three repeated measurements with adequate rest intervals, and calculation of objective quantitative indices—demonstrates methodological rigor.

Clinical Relevance

The research addresses an important gap in post-COVID knowledge by investigating neurologically **asymptomatic patients** who have recovered from moderate to severe disease. This distinction is clinically valuable, as it suggests cerebrovascular impairment may persist despite apparent clinical recovery and normal neurological examination. The focus on implications for critical care and perioperative settings provides practical significance for clinicians managing post-COVID patients.

Appropriate Control Group

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

The selection of ASA I-II controls without prior COVID-19 infection serves as a reasonable comparison group. The matching of baseline characteristics (age, sex, comorbidities) between groups minimizes potential confounding variables.

Clear Findings

The results show **consistent and statistically significant differences** across multiple parameters: lower baseline velocities (systolic, diastolic, and mean flow velocities, $p<0.001$) and markedly impaired vasodilatory response to the breath-holding test in post-COVID patients.

Methodological Limitations

Sample Size and Generalizability

The study includes only 50 post-COVID patients from a single center, which is **modest for establishing generalizable findings**. The authors acknowledge that 14 of 64 consenting participants were excluded due to inadequate acoustic windows, potentially introducing selection bias. The single-center design in a Moroccan military hospital may limit applicability to other populations, healthcare settings, and geographic regions.

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

Temporal Considerations

The study lacks **longitudinal follow-up data**, making it impossible to determine:

- Whether CVR impairment is permanent or reversible
- The trajectory of recovery over extended periods
- Whether the timing of measurement (3 months post-infection) represents the nadir or plateau of dysfunction

The Inclusion criterion of "within 3 months" of infection is relatively brief; longer-term studies are needed to characterize the natural history of this dysfunction.

Breath-Holding Test Limitations

The breath-holding test relies on **voluntary cooperation**, introducing potential variability. While the authors averaged three consecutive measurements to minimize this, the test may not reliably induce consistent hypercapnia across all participants. Factors such as compliance, anxiety, and individual variation in breathing patterns could influence results. The study reports that participants could not maintain 30 seconds of apnea in some cases (mean BHT 26.8-27.6 seconds), yet the analysis treats these as equivalent stimuli.

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

Confounding Variables

Although the authors report similar baseline medical histories between groups, several potential confounders deserve greater consideration:

- **Medication effects**: While exclusion criteria mention β-blockers and calcium-channel blockers, the paper does not detail what medications post-COVID patients were actually taking at the time of measurement

- **Residual inflammation**: No inflammatory markers (C-reactive protein, IL-6, D-dimer) were measured to quantify the degree of ongoing inflammation

- **Timing of measurement relative to infection**: Patients measured at 1 month versus 3 months post-infection may have substantially different CVR profiles, but subgroup analysis is not presented

- **Disease severity classification**: The paper categorizes COVID-19 as "moderate or severe" requiring hospitalization but does not provide specific severity metrics (oxygen requirements, ICU admission, mechanical ventilation) that could stratify outcomes

Control Group Heterogeneity

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

The control group of patients presenting for elective surgical procedures may represent a selection bias. These individuals may have different cardiovascular profiles or health trajectories than the general population. Additionally, the exclusion of participants with "uncontrolled cardiovascular or respiratory disorders" from the post-COVID group but no comparable exclusion from controls could introduce group imbalance.

Technical and Statistical Considerations

CVR and BHI Calculation

While the formulas for CVR [(Vm_after – Vm_before)/Vm_before] and BHI [(Vm_after – Vm_before)/Vm_before]/BHT are standard, the biological interpretation requires context. The substantial differences in absolute velocity values (mean velocity increase from 63 to 73 cm/s in post-COVID versus 71 to 95 cm/s in controls) suggest potential differences in baseline hemodynamic status that may not be fully explained by endothelial dysfunction alone.

Statistical Analysis

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

The study appropriately uses both parametric (Student's t-test) and non-parametric (Mann-Whitney U) tests based on data distribution. However, the paper does not report:

- Confidence intervals for key findings
- Effect sizes beyond p-values
- Multivariable analysis to control for potential confounders (age, diabetes, hypertension, obesity)
- Power analysis or sample size justification

The presentation of results primarily through p-values without accompanying confidence intervals limits interpretation of the magnitude and precision of observed differences.

Comparison with Existing Literature

The authors appropriately situate their findings within existing research. The results align with studies by Sonkaya et al. (COVID-19 patients with neurological symptoms showed higher velocities and lower CVR) and Marcic et al. (lower cerebral velocities and BHI in recovered mild COVID-19 patients). However, the distinction that this study examines **asymptomatic recovered patients** with moderate-to-severe disease represents a meaningful contribution.

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

The mechanistic explanation—that SARS-CoV-2 causes endothelial dysfunction through ACE2 receptor binding and inflammatory pathways—is well-supported by the literature, particularly postmortem studies showing microvascular lesions without viral RNA in brain tissue.

Implications and Practical Application

Clinical Significance

The authors propose that routine TCD assessment could identify post-COVID patients at risk for cerebrovascular complications during anesthesia or critical illness. This is a reasonable hypothesis, but the study does not demonstrate clinical outcomes—it identifies an **association, not a causal relationship or proven predictive value**. Prospective studies linking CVR impairment to actual adverse events (perioperative stroke, delirium, hypoperfusion) would substantially strengthen clinical recommendations.

Study Limitations Acknowledged

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

The authors transparently acknowledge key limitations: small sample size from a single center, lack of longitudinal follow-up, and variability inherent in the breath-holding test. This intellectual honesty is commendable, though it underscores that conclusions should be considered preliminary rather than definitive.

Critical Gaps and Recommendations for Future Research

1. **Longitudinal design**: Repeat TCD measurements at 6 months, 12 months, and beyond to characterize CVR recovery trajectories and identify whether dysfunction is reversible

2. **Mechanistic investigation**: Incorporate biomarkers of endothelial dysfunction (endothelial microparticles, von Willebrand factor, asymmetric dimethylarginine) and inflammatory markers to correlate with CVR impairment

3. **Larger sample sizes**: Multi-center studies with adequate power to detect clinically meaningful differences and conduct subgroup analyses by COVID-19 severity, age, and comorbidities

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

4. **Standardized CVR methodology**: Compare breath-holding test with alternative CVR assessment methods (CO_2 inhalation, acetazolamide) to validate findings

5. **Clinical outcomes**: Prospective cohort studies tracking perioperative and critical care outcomes in post-COVID patients stratified by CVR status

6. **Control group refinement**: Include age-matched, healthy community controls rather than surgical patients to ensure comparable baseline health status

7. **Functional neuroimaging**: Correlate TCD findings with advanced imaging (functional MRI, positron emission tomography) to localize vascular dysfunction and assess impact on cerebral perfusion

Conclusion

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT

This research presents **valuable preliminary evidence** that cerebrovascular reactivity remains impaired in asymptomatic patients recovering from moderate-to-severe COVID-19, suggesting persistent endothelial dysfunction. The study is methodologically sound in several respects, particularly the standardized single-operator TCD protocol and homogeneous study population.

However, the **modest sample size, single-center design, cross-sectional nature, and lack of clinical outcome data** prevent definitive conclusions about the clinical significance of this finding. The work would be substantially strengthened by longitudinal follow-up, larger patient cohorts, mechanistic biomarker integration, and demonstration of actual adverse clinical outcomes associated with CVR impairment.

The study is best viewed as a **hypothesis-generating investigation** that identifies an interesting physiological abnormality in post-COVID patients and justifies larger, multi-center studies to determine whether routine CVR assessment should be integrated into perioperative or critical care management of this population. Clinicians should exercise cautious interpretation and avoid overreliance on this single-center study for policy decisions regarding TCD screening in post-COVID patients until corroborating evidence from larger cohorts and studies with clinical outcome data become available.

ISSN: 2320-5407
International Journal of Advanced Research
Publisher's Name: Jana Publication and Research LLP
www.journalijar.com

REVIEWER'S REPORT