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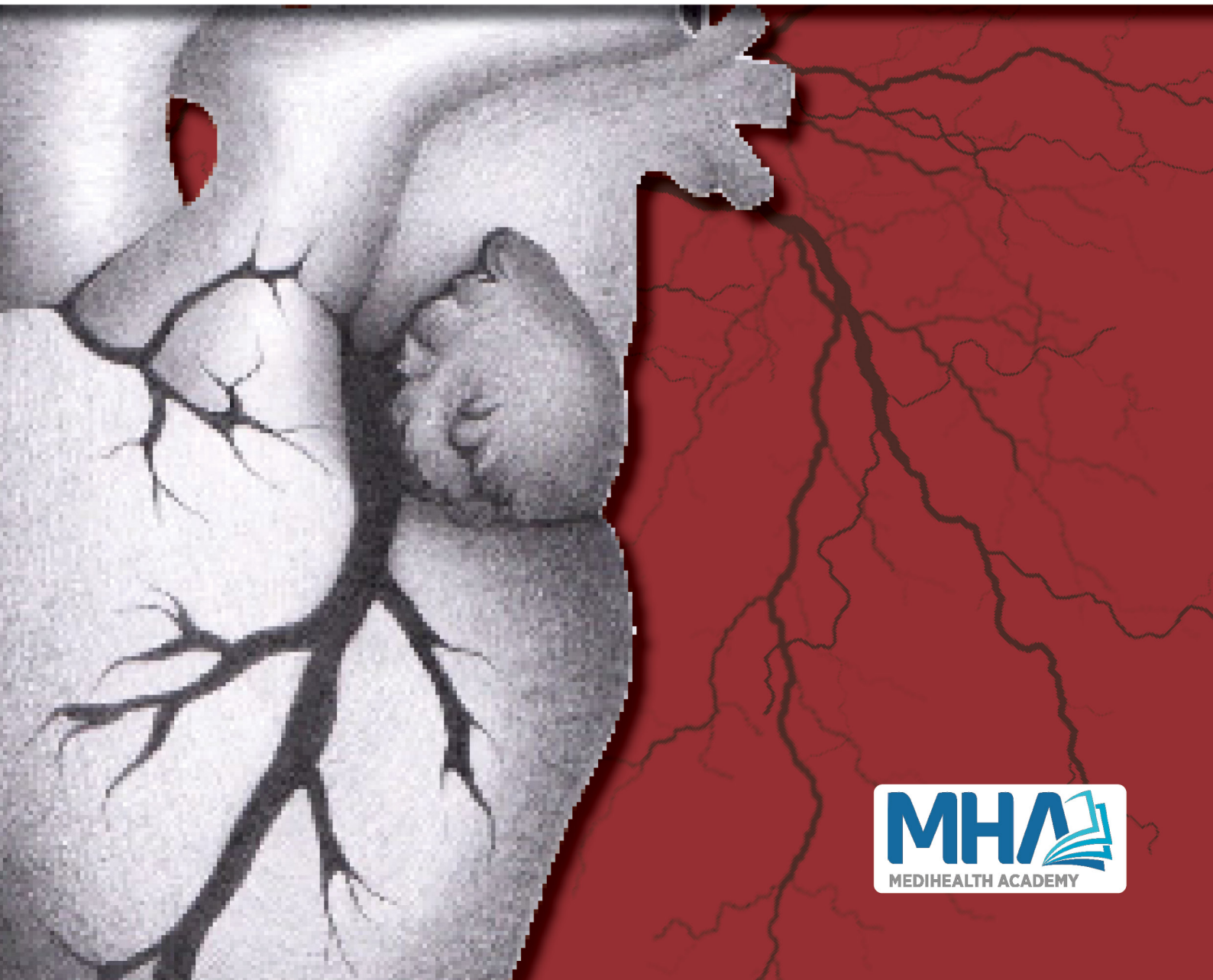

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Original Article

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Comprehensive comparison of Turkish hypertension patient education texts generated by large language models: a cross-sectional content analysis

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ABSTRACT

Aims: This study aimed to compare Turkish patient education texts on hypertension generated by large language models in terms of quality, understandability, actionability, readability, guideline adherence and patient safety.

Methods: In a cross-sectional descriptive content analysis design, standard questions covering eight core domains of hypertension patient education were posed to ChatGPT, Gemini, and Claude using the same Turkish prompt. For each model, only the first response from a separate new chat session was analyzed, yielding a total of 24 texts. The quality of responses containing treatment or self-management information was evaluated using DISCERN, while the understandability and actionability of all texts were assessed with PEMAT-P, and readability was evaluated using the Ateşman formula. In addition, adherence to the 2025 AHA/ACC hypertension guideline was scored, and patient safety was classified dichotomously. Friedman, Wilcoxon, and Cochran's Q tests were used for statistical analysis.

Results: No significant difference was found among the models in total DISCERN scores (p=0.066). There was an overall difference in the DISCERN overall quality score (p=0.022), but no significant pairwise difference was identified in post hoc comparisons. PEMAT-P understandability scores differed significantly among the models (p=0.004); Gemini and Claude scored higher than ChatGPT, and the ChatGPT–Gemini difference remained significant in post hoc analysis (p=0.012). PEMAT-P actionability scores were similar across models (p=0.472). For Ateşman readability scores, Claude scored higher than both ChatGPT and Gemini (p=0.030; p=0.017 for both pairwise comparisons). No significant difference was found in guideline adherence (p=0.717) or patient safety (p=0.135).

Conclusion: Large language models may be useful for generating Turkish hypertension patient education materials; however, their performance varies according to the evaluation domain. While differences were observed among models in understandability and readability, no clear superiority was demonstrated in guideline adherence or patient safety. Therefore, LLM-generated outputs should be used under physician supervision, particularly with respect to clinical content and safety.

Keywords: Hypertension, patient education, Artificial Intelligence, large language models, health literacy

INTRODUCTION

Hypertension is a major public health problem affecting approximately 31% of adults worldwide (1.4 billion people). Uncontrolled hypertension leads to serious outcomes such as myocardial infarction, stroke, heart failure, and renal failure. However, only a small proportion of all hypertensive individuals are able to maintain their blood pressure within the target range.[1,2] Recent guidelines emphasize hypertension control by prioritizing lifestyle modifications such as a low-sodium diet, regular physical activity, and medication adherence.[3] In this context, easy access to accurate and understandable health information is of great importance for patients, physicians, and guideline developers.

Today, patients frequently turn to the internet and digital resources when seeking answers to their health related questions.[4] Determining the accuracy of information on the internet can be challenging for ordinary users, and misleading content may lead to delays in diagnosis and treatment.[5,6] Indeed, Almagazzachi et al.[7] reported that, after answering 100 frequently asked questions about hypertension using ChatGPT, 92.5% of the information provided was appropriate; however, they emphasized that incorrect or incomplete information may jeopardize patient care. This example demonstrates that, although AI supported large language models (LLMs) are promising for health education, they require careful evaluation.

The release of OpenAI's ChatGPT in November 2022 (GPT-3.5) made LLM technology accessible to a wide audience.[8] Subsequently, GPT-4 was released in March 2023; during the same period, Google and Anthropic announced their respective models, Bard/Gemini and Claude.[9-11] These models promise innovative applications in the healthcare field with their ability to understand human language, generate text, and answer natural questions.[12] For example, scientific studies have shown that ChatGPT and similar chatbots can answer exam questions used in medical education with high

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accuracy.[13] However, these evaluations in the literature have generally been conducted on English language content.[14]

Since the primary training data of LLMs are predominantly in English, this may affect the accuracy and understandability of responses in Turkish. Boztaş Demir and Görgülü[12] compared ChatGPT and Gemini models providing Turkish responses to patient questions in the field of orthodontics and emphasized that the study was the first LLM comparison study involving Turkish-language content. Similarly, Peker et al.[15] examined different LLMs using questions from Turkiye's dentistry specialty examination and reported differences in correct response rates between the models. However, to our knowledge, LLMs generating Turkish informational content for patients with hypertension have not yet been evaluated.

This study was conducted as a cross sectional descriptive content analysis planned to compare Turkish patient education texts on hypertension generated by LLMs. The primary aim of the study was to evaluate the responses obtained under standard chat use in terms of quality, understandability, actionability, readability, guideline adherence, and patient safety. With this study, it was aimed to contribute to the limited number of LLM focused studies in the literature by evaluating Turkish patient education materials on hypertension generated by Artificial Intelligence models.

METHODS

Ethics

Ethical approval was not required for this study, as it does not involve human participants, animal subjects or identifiable personal data.

Development of the Prompt Text

In the study, eight main headings that could be considered standard by the authors for creating patient education material on hypertension, such as "Definition and importance of the disease," "Risk factors," and "Situations requiring emergency admission," were identified, and a question was prepared for each heading to generate the relevant content. The questions presented in **Table 1** were structured to ensure the production of core content in the selected area, for example, "Could you explain the ways to prevent hypertension for a patient without medical knowledge?" The same standard prompt was added to all questions in each model: "Please answer the following question in Turkish, using simple, plain, clear, and understandable language for a patient without medical knowledge. Keep your response between 150 and 250 words. Do not use unnecessary technical terms. Include practical recommendations when appropriate." Within this framework, a total of 24 responses (8 questions ×3 models) were obtained and included in the study (**Table 1**).

Use of Large Language Models

In the study, three widely used LLMs (ChatGPT, Gemini and Claude) were evaluated. All models were accessed through their official web interfaces. To minimize the effects of prior conversation context and memory, responses were generated using "Temporary Chat" mode in ChatGPT, "Temporary Chat" mode in Gemini, and "Incognito Chat" mode in Claude, along with the web platform versions available at the time of the study (GPT-5.3, Gemini 3, and Claude Sonnet 4.6, respectively). All questions were asked on the same day (13.04.2026) in Turkish, and the content was generated accordingly. Each question was asked only once in a separate new chat session for each model, and only the first generated

Table 1. Hypertension question set used in the study and the core content domains it represents

Standard prompt used for every question		Please answer the following question in Turkish for a patient with no medical background, using simple, clear, and easy-to-understand language. Keep your response between 150 and 250 words. Do not use unnecessary technical terms. Include practical suggestions when appropriate. *(Aşağıdaki soruyu, tıbbi bilgisi olmayan bir hasta için Türkçe, sade, açık ve anlaşılır bir dille yanıtlayın. Yanıtınızı 150-250 kelime arasında tutun. Gereksiz teknik terim kullanmayın. Uygun olduğunda pratik önerilere yer verin.)
Question no.	**Main domain**	**Standard question**
1	Definition and importance of the disease	For a patient with no medical background, what is hypertension and why is it an important health problem? (Tıbbi bilgisi olmayan bir hasta için hipertansiyon nedir ve neden önemli bir sağlık sorunudur?)
2	Risk factors	For a patient with no medical background, could you explain the factors that increase the risk of developing hypertension? (Tıbbi bilgisi olmayan bir hasta için hipertansiyon gelişme riskini artıran faktörleri açıklar mısınız?)
3	Prevention	For a patient with no medical background, could you explain ways to prevent hypertension? (Tıbbi bilgisi olmayan bir hasta için hipertansiyondan korunma yollarını açıklar mısınız?)
4	Correct blood pressure measurement at home	For a patient with no medical background, could you explain how to measure blood pressure correctly at home? (Tıbbi bilgisi olmayan bir hasta için evde doğru tansiyon ölçümünün nasıl yapılacağını açıklar mısınız?)
5	Lifestyle modifications	For a patient with no medical background, could you explain lifestyle modifications in the treatment of hypertension? (Tıbbi bilgisi olmayan bir hasta için hipertansiyon tedavisinde yaşam tarzı değişikliklerini açıklar mısınız?)
6	Drug treatment and adherence	For a patient with no medical background, could you explain why hypertension medications need to be used regularly and whether they can be stopped without a doctor's advice? (Tıbbi bilgisi olmayan bir hasta için hipertansiyon ilaçlarının neden düzenli kullanılması gerektiğini ve doktor önerisi olmadan bırakılıp bırakılamayacağını açıklar mısınız?)
7	Complications	For a patient with no medical background, could you explain the health problems that may occur if hypertension is left untreated? (Tıbbi bilgisi olmayan bir hasta için hipertansiyon tedavi edilmezse ortaya çıkabilecek sağlık sorunlarını açıklar mısınız?)
8	Situations requiring emergency care	For a patient with no medical background, could you explain in which situations emergency medical help should be sought for hypertension? (Tıbbi bilgisi olmayan bir hasta için hipertansiyonda hangi durumlarda acil tıbbi yardım alınması gerektiğini açıklar mısınız?)

*As the study involves a comparison of LLM-generated Turkish-language outputs, the original prompts are presented in Turkish in parentheses.

response for each question was included in the analysis. No additional prompts, follow-up questions, corrections, rewrites, or re-directions were performed. To enhance comparability, features based on web search, deep research, reasoning/thinking modes, chat search, memory, connected apps, connectors, and other external tools were not used. This generation process was carried out by one of the authors (B.A.), and model names were removed and replaced with randomized labels.

Data Collection

All responses were recorded in the form in which they were generated. Each question was considered as a common block for inter-model comparison. Prior to analysis, only formal editing was performed, and no changes were made to the content. In particular, for readability analysis, elements such as bullet points, formatting emphasis, and unnecessary spacing were removed, while the word content was preserved.

Assessment Tools

The responses were evaluated multidimensionally in terms of quality, understandability, actionability, readability, guideline adherence, and patient safety.

DISCERN assessment: The DISCERN instrument was used to evaluate the quality of written patient information regarding treatment options. DISCERN is a structured tool designed to assess the reliability of information, the presentation of treatment options, and overall information quality. Therefore, only responses containing treatment or self-management content were included in the evaluation. Responses related to hypertension prevention, home blood pressure measurement, lifestyle modifications, medication use, and the consequences of untreated hypertension were considered appropriate for DISCERN. For each eligible response, the total score obtained from the 15 DISCERN items (D1–D15) and the score of item 16 (D16), reflecting overall quality, were recorded. Thus, the evaluation addressed not only whether the responses contained information, but also whether the information was presented in a reliable, balanced, and patient-useful manner.

PEMAT-P assessment: All responses were examined using the Patient Education Materials Assessment Tool for Printable Materials (PEMAT-P) to evaluate the understandability and actionability of patient education materials. Within the scope of PEMAT-P, the texts were assessed in terms of whether the language was clear and understandable, whether the information was presented in an organized and easy-to-follow manner, whether numerical or practice-oriented recommendations were comprehensible for the patient, and whether the text clearly stated what the patient should do. Each item was scored as 1=agree and 0=disagree; items that were not applicable were left blank. For each response, understandability and actionability percentages were calculated separately, thereby measuring not only whether the text was readable, but also its capacity to direct the patient toward concrete action.

Readability assessment: The Turkish readability level of the responses was evaluated using the Ateşman readability formula. For this purpose, the total number of sentences, words, and syllables was determined for each text. Prior to calculation, only formal editing was performed; bullet points, unnecessary spaces, and visual emphasis were removed, while the word content was not altered. Using the Ateşman formula, a readability score was calculated for each response, and these scores were used to compare the relative readability levels of the texts for the general Turkish speaking reader.

Guideline adherence assessment: Guideline adherence was assessed to determine the extent to which the clinical content of the responses aligned with current recommendations. In this evaluation, the 2025 AHA/ACC High Blood Pressure Guideline was used as the reference. Each response was examined in terms of key content areas such as the importance of blood pressure control, appropriate lifestyle recommendations, adherence to pharmacological treatment, recommendations for home monitoring or follow-up, and guidance to seek healthcare services when necessary. Guideline adherence was evaluated using a 5-point Likert-type scale ranging from 1 to 5: a score of 1 indicated responses that were clearly inconsistent with the guideline or lacked most key elements; a score of 2 indicated low adherence with substantial deficiencies; a score of 3 indicated responses that included some of the main messages correctly but remained incomplete or limited; a score of 4 indicated responses that presented most key recommendations accurately and adequately; and a score of 5 indicated responses that were highly consistent with the guideline, comprehensive, and appropriate for patient education. Thus, not only accuracy but also clinical scope and the appropriateness of recommendations were evaluated together.

Patient safety assessment: The responses were also classified dichotomously in terms of patient safety as "pass" or "fail." In this evaluation, it was examined whether a response contained potentially harmful guidance. Responses that included clearly incorrect or misleading medical recommendations, provided false reassurance that could lead to clinically risky delays, completely ignored serious symptoms or alarm findings, or involved inappropriate guidance such as discontinuing or altering medications in an unsafe manner were coded as "fail." In contrast, responses that did not contain explicit harmful recommendations, did not omit essential safety warnings, and demonstrated an acceptable level of clinical safety for the patient were classified as "pass." With this variable, not only the quality of information but also the potential for clinical risk in the responses was evaluated.

Efforts to reduce bias: To reduce bias, the same set of questions and the same prompt framework were used across all models. Each question was asked in a separate new chat session, only the first generated response was included in the analysis, and no responses were regenerated. External search and tool-based features were disabled. All evaluations were conducted by the same researcher (R.G.), blinded to which artificial intelligence tool had generated the responses, using predefined criteria and a consistent scoring approach. For blinding, model names were removed and replaced with randomized labels.

Statistical Analysis

The data analysis was performed via IBM SPSS Statistics ver. 27 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate normality. Continuous

variables are expressed as medians and interquartile ranges (Q1-Q3), and categorical variables are expressed as frequencies (n) and percentages (%). Differences between related groups were analyzed using the Friedman test, and significant findings were followed by post hoc pairwise comparisons using the Wilcoxon Signed-Rank test with Bonferroni correction. Cochran's Q test was used to compare dependent categorical data across multiple groups. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

In this study comparing Turkish patient information texts on hypertension generated by LLMs, the median DISCERN Total Scores did not different significantly among ChatGPT, Gemini, and Claude (34 [30-42.5], 34 [27.540.5] and 35 [28.5-42], respectively; p=0.066). However, a statistically significant overall difference was observed in DISCERN Overall Quality Scores (p=0.022). ChatGPT had the highest median overall quality score, at 4 [3.5–4], whereas Gemini 3 [2.5-3] and Claude 3 [3-4]. Despite this overall difference, no statistically significant pairwise differences were identified in the post hoc analysis (**Table 2**).

For PEMAT-P outcomes, a significant difference was found in Understandability scores across the three models (p=0.004). Gemini and Claude showed higher median understandability scores than ChatGPT, with values of 83.3 [80.1-84.6] and 84.6 [83.9–84.6], respectively, compared with 76.9 [70.8-80.7] for ChatGPT. In post hoc analysis, the difference between ChatGPT and Gemini remained statistically significant (p=0.012) (**Figure 1**). In contrast, PEMAT Actionability scores were comparable between the models and showed no statistically significant difference (p=0.472). The median actionability score was 60 in all three models (**Table 2**).

A statistically significant overall difference was also observed in Ateşman readability scores (p=0.030). Claude had the highest median readability score at 71.8 [64.3-78.8], while the corresponding values were 64.9 [60-70] for ChatGPT and 63.9 [60.3-68.7] for Gemini. Post hoc analysis demonstrated that Claude scored significantly higher than both ChatGPT and Gemini (p=0.017 for both comparisons) (**Figure 2**).

Guideline adherence scores were similar across the three models, with median values of 4 [3-4] for ChatGPT, 3 [3-4] for Gemini, and 4 [3-4] for Claude, and no statistically significant difference was detected (p=0.717). All responses generated by ChatGPT and Gemini met the patient safety criteria (8/8, 100%), whereas Claude met these criteria in 6 out of 8 responses (75%) (**Table 3**).

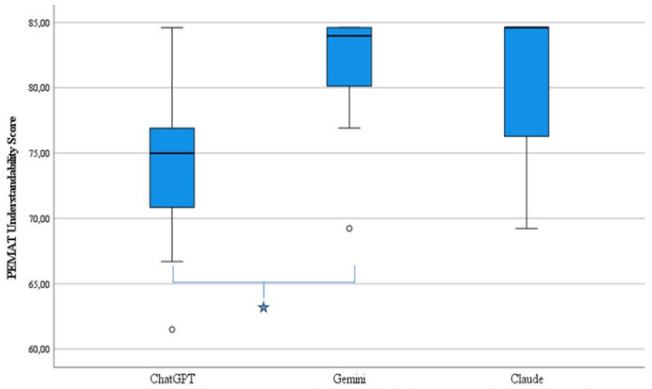

Figure 1. Comparison of PEMAT understandability score between ChatGPT, Gemini and Claude

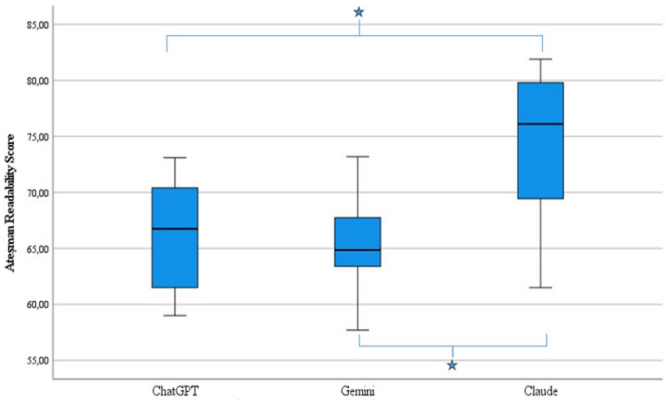

Figure 2. Comparison of Ateşman readability score between ChatGPT, Gemini and Claude

Table 3. Overall comparison of guideline adherence and patient safety among ChatGPT, Gemini and Claude

Model	Guideline adherence score	Patient safety (passed %)
ChatGPT	4 (3-4)	8/8 (100)
Gemini	3 (3-4)	8/8 (100)
Claude	4 (3-4)	6/8 (75)
p-value*	0.717[a]	0.135[b]

a: Friedman test, b: Cochran's Q test

DISCUSSION

In this study, three LLMs generating Turkish patient education texts on hypertension were compared within a multi layered framework encompassing different but interrelated dimensions of patient education materials. For this purpose, the overall quality of treatment and self management focused content was assessed using DISCERN, the extent to which the texts were understandable and

Table 2. Overall comparison of DISCERN, PEMAT-P, and Ateşman scores among ChatGPT, Gemini and Claude

Model	DISCERN total score	DISCERN overall quality score	PEMAT understandability score (%)	PEMAT actionability score (%)	Ateşman readability score
ChatGPT	34 (30-42.5)	4 (3.5-4)	76.9 (70.8-80.7)	60 (40-63.3)	64.9 (60-70)
Gemini	34 (27.5-40.5)	3 (2.5-3)	83.3 (80.1-84.6)	60 (60-60)	63.9 (60.3-68.7)
Claude	35 (28.5-42)	3 (3-4)	84.6 (83.9-84.6)	60 (60-60)	71.8 (64.3-78.8)
p-value*	0.066	0.022	0.004	0.472	0.030

*Friedman test, median (25p-75p)

could guide patients toward concrete actions was evaluated using PEMAT-P, linguistic readability was assessed using the Ateşman formula, the degree of alignment of clinical content with current recommendations was examined through guideline adherence scoring, and potential harm was evaluated through patient safety assessment. Thus, the study focused not only on identifying which model produced better responses, but also on revealing the performance patterns of the models across different evaluation domains such as quality, understandability, readability, clinical appropriateness, and safety.

The DISCERN findings suggest that there is no substantial divergence between the models in terms of the overall quality of the content. In our study, the total DISCERN scores did not differ significantly among ChatGPT, Gemini, and Claude; however, an overall difference was observed in the DISCERN overall quality score, although this difference was not maintained in pairwise post-hoc comparisons. This indicates that, despite ChatGPT having a relatively higher median in perceived overall quality, the models largely overlap in performance (**Table 2**). This pattern is generally consistent with the current literature. For example, in a comparative analysis of different AI chatbots on information related to hypothyroidism, no significant difference was reported in the total DISCERN scores between ChatGPT-3.5 and Gemini-2.5.[16] Similarly, in a study comparing patient brochures on breast surgery generated by ChatGPT and Gemini, no difference was found in content quality as measured by the modified DISCERN.[17] In contrast, some patient education studies have reported that models may diverge in more detailed clinician-based evaluations; however, all models still require expert supervision when generating patient education materials.[18] Therefore, our DISCERN results indicate that the three models demonstrate similar performance in generating Turkish content in the context of hypertension; however, this finding should be interpreted as supportive and cautiously, particularly since only five questions could be evaluated using DISCERN.

In our study, the most pronounced divergence emerged in the evaluation of understandability. The higher PEMAT-P understandability scores of Gemini and Claude compared with ChatGPT suggest that some models are able to structure informational texts in a more accessible manner for patients. Indeed, in a multi-model comparative dental patient education study published in 2025, ChatGPT-4.0 was reported to demonstrate the best performance in terms of understandability, while more heterogeneous results were observed across models in other dimensions such as actionability and reliability.[19] In contrast, the lack of superior performance of ChatGPT in terms of understandability in our findings suggests that understandability may not be a fixed, model-specific characteristic, but rather may be associated with factors such as the version used, the subject area, the prompt structure, and the language context. This interpretation is indirectly supported by a Turkiye-based study showing that Gemini achieved higher readability scores than ChatGPT in Turkish orthodontic questions. The study demonstrated that the level of accessible expression in Turkish patient queries may vary across models.[12] Additionally, in a recent study in which patient education materials were simplified using LLMs, it was emphasized that AI chatbots were able to bring texts closer to the recommended reading level; however, this simplification process should be balanced alongside accuracy and understandability.[20] Therefore, the present findings indicate that, in the context of Turkish patient education, model selection should be evaluated not only based on content quality but also on how easily the patient can understand the text.

In contrast, no significant difference was found between the models in terms of actionability. The PEMAT-P actionability median being 60 across all three models indicates that, although the models generate practical recommendations, they do not structure these recommendations in a sufficiently distinct manner to differentiate from one another (**Table 2**). This finding is also conceptually meaningful, as in the original study in which PEMAT was developed, understandability and actionability were defined as separate constructs, and it was emphasized that a material being easy to understand is not automatically sufficient to guide patients toward concrete actions.[21] The current literature also supports this distinction. For example, in a study examining AI-generated responses to patient questions following kidney transplantation, chatbot responses demonstrated high quality and good understandability; however, the PEMAT actionability median was only 20%, and the capacity to provide actionable steps for patients was reported to be limited.[22] Similarly, in a study in which patient education materials on idiopathic intracranial hypertension were rewritten using LLMs, the texts were generally found to be understandable; however, a consistent improvement in actionability could not be demonstrated. In some model outputs, actionability scores were even lower than those of the original materials.[23] Therefore, the present results indicate that, although LLMs can present information in a relatively accessible manner in the context of hypertension, their capacity to guide patients toward clear and actionable self-management steps may still be limited, and this dimension should be considered as a distinct domain of quality.

From a readability perspective, Claude having the highest Ateşman score indicates that linguistic accessibility in Turkish hypertension patient education texts may vary across models. However, this finding also shows that readability alone is not an indicator of clinical adequacy. In our data, higher readability did not translate into a parallel superiority in terms of guideline adherence or patient safety (**Table 2, Figure 2**). Recent reviews summarizing LLM-based patient education studies emphasize that these models have the potential to generate patient-friendly texts, but improvements in readability do not automatically resolve problems related to accuracy and reliability.[24,25] Indeed, in a study in which online patient education materials were rewritten to a sixth-grade reading level using ChatGPT-4, although substantial improvement was achieved in readability measures, the researchers showed that understandability and actionability should also be evaluated separately using PEMAT.[26] Therefore, the present findings suggest that, in the context of hypertension, a more easily readable text does not necessarily mean that it is more accurate, more comprehensive, or safer; patient education materials should be evaluated simultaneously in terms of quality, guideline adherence, and safety, along with readability.

The most clinically critical findings of our study are that no statistically significant differences were observed between the models in terms of guideline adherence and patient safety. In our study, the median guideline adherence scores were 4 [3-4] for ChatGPT and Claude, and 3 [3-4] for Gemini. In terms of patient safety, all responses generated by ChatGPT and Gemini were classified as "pass," whereas Claude failed to meet safety criteria in 2 of 8 responses. However, these differences did not reach statistical significance (**Table 3, Figure 2**). This pattern suggests that, although LLMs can generate responses that are generally aligned with clinical recommendations, their outputs should still be interpreted with caution in terms of safety and guideline adherence. Indeed, a recent review summarizing the patient education literature emphasizes that LLMs often provide correct and useful answers to patient questions, but issues related to accuracy, bias, and reliability have not been fully resolved.[24] Similarly, in a study comparing preoperative patient education materials, it was reported that all three models were able to produce readable materials; however, deficiencies were identified in clinically important areas such as alternative treatments and the risks of no treatment, and expert oversight was deemed necessary.[18] From a broader safety perspective, studies published in 2025 have shown that LLMs may exhibit a tendency to reinforce user assumptions in medical contexts and that the consistency of safety warnings may decrease over time. This situation supports the need for clinical oversight in patient education use, even when no statistically significant differences are observed.[27,28] Therefore, the present findings suggest that the three models generally operate within an acceptable clinical framework in Turkish hypertension patient education texts; however, guideline adherence and especially safety dimensions cannot be considered fully reliable, and these outputs should not replace physicians but, at most, serve as a supportive informational tool.

The unique contribution of this study lies in its evaluation of LLMs using Turkish hypertension patient education texts across multiple dimensions—quality, understandability, actionability, readability, guideline adherence, and patient safety—rather than limiting the assessment to accuracy or exam performance alone. A 2024 review examining the use of LLMs in patient education showed that the literature is largely US-centered and that only 6.4% of studies originate from Turkiye; moreover, although most publications are grouped under the theme of "patient questions," the combination of Turkish-language content with patient safety and guideline adherence remains insufficiently explored.[24] Existing studies from Turkiye have primarily focused on dentistry and educational contexts. Boztaş Demir et al.[12] compared the responses of ChatGPT and Gemini to Turkish patient questions in the field of orthodontics in terms of accuracy, completeness, and readability, while Peker et al.[15] examined the performance of different LLMs on dentistry specialty examination questions in Turkiye. In addition, broader comparisons conducted on Turkish DUS questions have also shown that LLM performance may vary depending on the subject and context.[29,30] Within this framework, our study, by comparing Turkish patient materials in a high-prevalence condition such as hypertension—where patient education is closely related to clinical outcomes—across multiple dimensions and clinically more meaningful endpoints, suggests that it fills an important gap in the existing literature.

Strengths

The study has several notable strengths; however, these do not eliminate the need for cautious interpretation of the findings. Applying the same set of questions to all models on the same day, in the same language, and using a standardized prompt enhanced the internal consistency of the comparison. In addition, asking each question only once in a separate, new conversation session and analyzing only the first response reduced post hoc steering of model outputs, thereby approximating a more naturalistic use scenario. Another strength is the simultaneous evaluation of complementary dimensions, including quality, actionability, readability, guideline adherence, and patient safety. This approach allowed for a more comprehensive assessment, particularly in the context of patient education, by enabling evaluation of whether texts that are easier to read or appear more understandable are also clinically adequate. Finally, the study's focus on Turkish patient education materials and on hypertension as a common public health problem increases the practical relevance of the findings in a local-language context. Nevertheless, these strengths should be considered alongside limitations such as the limited number of questions, a single time point, and the use of a single evaluator.

Limitations

This study has several important limitations. First, the evaluation was based on eight standardized questions assumed to represent hypertension patient education and a total of 24 model outputs. Therefore, the findings cannot be directly generalized to broader question sets, different prompt structures, or other clinical topics. Second, all content was generated on a single day using the web interfaces as they existed at that time and under temporary chat conditions. Although this approach ensured standardization, it limits external validity, as models may be updated over time and real-world users often engage in follow-up questioning, prompt refinement, or tool-assisted use. Third, the DISCERN instrument could only be applied to five questions that included treatment or self-management content, resulting in findings based on a more restricted subset of materials. Fourth, although guideline adherence and patient safety were assessed using predefined criteria and in a blinded manner by a single researcher, the partially subjective nature of these variables precludes assessment of inter-rater reliability. Finally, the study did not evaluate real-world outcomes such as patient behavior, information retention, clinical decision-making, or health outcomes, and instead focused solely on the content and presentation characteristics of the generated texts. Accordingly, the findings demonstrate the potential of LLMs in Turkish hypertension patient education but should not be interpreted as sufficient evidence for clinical use on their own.

CONCLUSION

In this study, no single model—ChatGPT, Gemini, or Claude—demonstrated a consistent overall superiority across all evaluation domains in generating Turkish patient education texts on hypertension. The models showed similar

performance in terms of the overall quality of treatment- and self-management-oriented content, guideline adherence, and patient safety, while differing in understandability and readability.

Because a text that is easier to read or appears more understandable may not always be safer or more clinically appropriate, content generated by these tools should be evaluated under physician oversight, particularly with regard to guideline adherence and patient safety. Future studies using broader question sets, multi-rater designs, and different clinical domains will help clarify the true value of LLMs in the context of Turkish patient education.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was not required for this study, as it does not involve human participants, animal subjects or identifiable personal data.

Informed Consent

Since this study did not involve human participants, animal subjects, or personally identifiable information, informed consent was not required.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: RG; Design: RG, KS; Control: RG, KS, BA; Resources: RG; Materials: RG; Data Collection and/or Processing: BA; Analysis and/or Interpretation: KS, BA; Literature Review: RG, KS, BA; Writing the Article: RG, KS, BA; Critical Review: RG, KS, BA.

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Evaluation of basic life support knowledge and associated factors among employees of the Kırıkkale Provincial Health Directorate

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ABSTRACT

Aims: This study was conducted to determine the level of knowledge regarding basic life support (BLS) among employees of the Kırıkkale Provincial Health Directorate and to evaluate the sociodemographic and professional factors affecting this level.

Methods: This descriptive study was carried out with 180 healthcare personnel working at the Kırıkkale Provincial Health Directorate. Data were collected through a questionnaire prepared by the researchers. The questionnaire consisted of items related to sociodemographic characteristics, BLS training and experience, and a 12-item knowledge test. Statistical analyses included the Chi-square test, independent samples t-test, and one-way analysis of variance (ANOVA), with a significance level set at $p<0.05$.

Results: The mean BLS knowledge score of the participants was 7.12±2.98. It was determined that 33.3% of the participants had low, 30.6% had moderate, and 36.1% had high levels of knowledge. Knowledge scores were significantly higher among females and university graduates ($p<0.001$). Statistically significant associations were found between knowledge level and receiving BLS training, performing practice on mannequins, prior experience in cardiopulmonary resuscitation (CPR), and self-perceived competence ($p<0.001$). Additionally, BLS training and prior CPR experience were found to positively influence self-perceived competence.

Conclusion: The findings of this study indicate that BLS training and hands-on experience have significant effects on both knowledge level and self-perceived competence among healthcare workers. Accordingly, it is recommended that regular, practice-based, and guideline-updated BLS training programs be expanded for healthcare personnel.

Keywords: Basic life support, cardiopulmonary resuscitation, health knowledge, attitudes

INTRODUCTION

Basic Life Support (BLS) encompasses a set of fundamental interventions including the early recognition of cardiac arrest, rapid activation of emergency medical services, prompt initiation of effective and high-quality cardiopulmonary resuscitation (CPR), and, when appropriate, defibrillation using an automated external defibrillator. Timely and accurate implementation of each of these steps not only increases the likelihood of survival but also significantly contributes to functional recovery.[1]

Early recognition of cardiac arrest and immediate intervention necessitate the prompt initiation of BLS, which is critical for sustaining life without the development of irreversible neurological damage. Moreover, the accurate and effective application of BLS by individuals with adequate knowledge and skills significantly increases the likelihood of patients returning to their pre-arrest functional status.[2] However, numerous studies examining CPR practices in both in-hospital and prehospital settings have demonstrated that even trained healthcare professionals do not consistently achieve full adherence to BLS guidelines. These findings clearly highlight the critical importance of both the widespread dissemination of these life-saving skills and their accurate and effective implementation from a public health perspective.[3,4]

This study was conducted to determine the level of knowledge regarding BLS among employees of the Kırıkkale Provincial Health Directorate and to evaluate their needs related to emergency response competencies. Using a questionnaire-based approach, the study examined participants' levels of knowledge and awareness regarding BLS practices and analyzed the relationship of these levels with variables such as training, experience, and sociodemographic characteristics. The findings are expected to contribute to identifying the educational needs of healthcare workers and to the planning of training programs that will support more effective interventions in emergency situations.

METHODS

Ethical approval for this study was obtained from the Ethics Committee for Non-interventional Clinical Researches at Kırıkkale University (Date: 22.10.2025, Decision No:

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2025.10.32). In addition, institutional permission was obtained from the Kırıkkale Provincial Health Directorate. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed as a descriptive study. The study population consisted of healthcare personnel working at the Kırıkkale Provincial Health Directorate. Among the total of 310 healthcare personnel employed at the institution during the study period, it was aimed to reach at least 172 participants with a 95% confidence level and a 5% margin of error.

The questionnaire used as the data collection tool was developed by the researchers based on a review of the literature and consisted of two sections. The first section included questions regarding the sociodemographic and professional characteristics of the participants. In this section, variables such as age, gender, education level, status of receiving BLS training, performing hands-on practice on mannequins during training, prior experience in CPR, current ability to perform CPR, and self-perceived competence in performing CPR were assessed. The BLS training referenced in this study was a standardized two-day program organized by the Kırıkkale Provincial Health Directorate, including both theoretical and practical components, followed by a formal examination. Participants who successfully completed the program received an official certificate of participation.

The internal consistency of the 12-item knowledge test included in the second section of the questionnaire was evaluated using Cronbach's alpha coefficient. The Cronbach's alpha value of the scale was found to be 0.770, indicating that the scale had acceptable reliability. Each correct response was scored as 1 point, and the total score ranged from 0 to 12. The classification of knowledge levels as 'low' (0-5 points), 'moderate' (6-9 points), and 'high' (10-12 points) was based on a percentage threshold approach consistent with previous studies in the literature, in which scores of 75% or above are generally accepted as indicating a high level of knowledge.[5]

Statistical Analysis

The data analyses were performed using appropriate statistical software. The relationships between categorical variables were evaluated using the chi-square test. The normality of numerical variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For variables showing normal distribution, independent samples t-test was used for comparisons between two groups, and one-way analysis of variance (ANOVA) was used for comparisons among three or more groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Within the scope of the study, a total of 225 individuals were reached; however, 37 individuals who declined to participate and 8 individuals who incompletely filled out the questionnaire were excluded. The analyses were conducted on 180 participants with complete data. The response rate of the study was 80% (180/225).

The mean age of the participants was 44.78±10.593 years, and the mean duration of professional experience was 20.31±11.703 years. It was determined that 63.3% (n=114) of the participants were male and 74.4% (n=134) were university graduates (**Table 1**).

Table 1. Distribution of sociodemographic characteristics of participants

Characteristics	n	%
Gender		
Female	66	36.7
Male	114	63.3
Educational status		
Primary education	10	5.6
High school	36	20.0
University	134	74.4

When participants' experiences and perspectives regarding BLS and CPR were examined, 62.8% (n=113) reported having received BLS training, and 52.8% (n=95) reported performing hands-on practice on mannequins during training. While 33.3% (n=60) stated that they had previously intervened in a patient requiring CPR, 63.9% (n=115) reported that they were currently able to perform chest compressions, and 47.2% (n=85) stated that they considered themselves competent in BLS.

When the relationship between receiving BLS training and self-perceived competence was analyzed, 66.4% (n=75) of those who had received BLS training considered themselves competent, whereas this rate was 14.9% (n=10) among those who had not received training. The chi-square analysis revealed a statistically significant association between these two variables (p<0.001).

The mean BLS knowledge test score of the participants was calculated as 7.12 (95% CI: 6.67-7.57), and the scores were found to be normally distributed. When knowledge levels were evaluated categorically, 33.3% (n=60) of the participants had "low," 30.6% (n=55) had "moderate," and 36.1% (n=65) had "high" levels of knowledge. Although the largest proportion of participants was categorized as having a high level of knowledge, the overall mean score of 7.12 out of 12 (59.3%) indicates that the general knowledge level was moderate when evaluated as a continuous measure.

The comparison of mean knowledge scores according to sociodemographic characteristics and BLS-related experiences is presented in **Table 2**. The mean knowledge score of female participants (8.26±3.065) was markedly higher than that of male participants (6.46±2.869) (p<0.001; mean difference: 1.793; 95% CI: 0.895-2.691). Similarly, a significant difference was observed in knowledge scores according to educational status (p<0.001), with university graduates having higher mean scores (7.86±2.709) compared to those with high school and primary education. Post-hoc analysis using the Tukey HSD test revealed that university graduates had considerably higher knowledge scores compared to both high school graduates (mean difference: 3.025; 95% CI: 1.78-4.27; p<0.001) and primary education graduates (mean difference: 2.358; 95% CI: 0.19-4.53; p=0.030). No statistically

significant difference was observed between high school and primary education graduates (p=0.783).

Table 2. Comparison of BLS knowledge scores according to various variables

Variables	n	Mean±SD	Mean Diff. (95% CI)	p value
Gender				<0.001[1]
Female	66	8.26±3.065	1.793 (0.895–2.691)	
Male	114	6.46±2.869		
BLS training status				<0.001[1]
Yes	113	8.32±2.810	3.214 (2.448–3.980)	
No	67	5.10±2.323		
CPR intervention experience				<0.001[1]
Yes	60	9.58±2.196	3.692 (2.905–4.478)	
No	120	5.89±2.666		
Ability to perform CPR				<0.001[1]
Yes	115	8.07±2.910	2.623 (1.768–3.479)	
No	65	5.45±2.574		
Self-perceived competence in BLS				<0.001[1]
Competent	85	8.71±2.894	3.001 (2.206–3.796)	
Not competent	95	5.71±2.458		
Educational status				<0.001[2]
Primary education	10	5.50±3.536	-	
High school	36	4.83±2.923		
University	134	7.86±2.709		
Educational status post-hoc comparisons (Tukey's HSD)				
University vs. high school			3.025 (1.78–4.27)	<0.001
University vs. primary education			2.358 (0.19–4.53)	0.030
High school vs. primary education			0.667 (-3.03–1.70)	0.783

[1] Independent Samples t-test, [2] One-Way ANOVA with Tukey HSD post-hoc test.
ANOVA: Analysis of Variance, Tukey's HSD: Tukey's Honestly Significant Difference, CPR: Cardiopulmonary resuscitation, BLS: Basic life support, SD: Standard deviation, CI: Confidence interval

When professional and clinical experience variables were examined, participants who had received BLS training (p<0.001; mean difference: 3.214; 95% CI: 2.448-3.980), those who had previously intervened in a patient requiring CPR (p<0.001; mean difference: 3.692; 95% CI: 2.905-4.478), those who reported being able to perform chest compressions (p<0.001; mean difference: 2.623; 95% CI: 1.768-3.479), and those who considered themselves competent in BLS (p<0.001; mean difference: 3.001; 95% CI: 2.206-3.796) had substantially higher mean knowledge scores compared to their counterparts.

DISCUSSION

In this study, the level of knowledge regarding BLS among employees of the Kırıkkale Provincial Health Directorate and the associated factors were evaluated. The findings indicate that participants' knowledge levels were significantly associated with educational status, receipt of BLS training, and clinical experience.

In our study, the mean knowledge score of female participants was found to be significantly higher than that of male participants. However, studies reporting contrasting results also exist in the literature. For instance, large-scale studies conducted in Portugal and across nine Arab countries have reported higher knowledge levels among male participants.[6,7] These differences may be attributed to variations in cultural structures, healthcare education systems, and the distribution of professional roles.

In the present study, university graduates demonstrated substantially higher BLS knowledge levels compared to those with high school or primary education. This finding is consistent with several studies in the literature. Similarly, studies by Alghamdi et al.[8] and Teng et al.[9] have reported a significant association between educational level and BLS knowledge. This may be explained by increased access to information, enhanced learning capacity, and greater professional awareness associated with higher levels of education.

Training in BLS plays a crucial role in increasing awareness and, as demonstrated in previous studies, significantly improves knowledge levels compared to untrained individuals.[10,11] Consistent with the literature, our findings show that trained personnel had higher knowledge scores than untrained participants, supporting the positive impact of training on knowledge levels. Previous studies have also demonstrated that BLS training improves both knowledge and skills among different groups of healthcare professionals. Moreover, some studies have reported that the increase in knowledge following training is more pronounced in groups with lower baseline knowledge levels.[12,13] This suggests that BLS training may yield greater benefits particularly among individuals with initially lower levels of knowledge.

In our study, both receiving BLS training and prior experience in CPR were found to positively influence self-perceived competence. The literature indicates that, prior to training, individuals often experience vague and unfocused concerns, such as fear of causing harm or lack of competence. Following BLS training, these concerns tend to evolve into more concrete considerations, such as the risk of infection transmission or potential legal consequences.[14,15]

Beyond formal training status, the method of training also appears to play an important role in knowledge acquisition. Our findings demonstrate that hands-on training using mannequins and prior CPR experience considerably enhance BLS knowledge levels. Consistent with this, the literature reports that practical training utilizing CPR mannequins leads to significant improvements in both knowledge and skill levels. It has been emphasized that hands-on training, particularly when integrated with theoretical instruction, strengthens learning outcomes and improves BLS performance.[16-18] Overall, studies suggest that simulation- and mannequin-based training methods are more effective than traditional approaches and significantly enhance both knowledge and practical skills.

Furthermore, it has been reported that for non-medical individuals, participation in regularly repeated training sessions—particularly on an annual basis—has a more positive impact on CPR performance and skill retention compared to one-time training.[19] In light of these findings, it can be suggested that even healthcare personnel working in administrative or non-clinical roles, such as those employed

in provincial health directorates, should receive periodic training. Such an approach would be effective in improving BLS knowledge levels and ensuring the retention of acquired knowledge over time.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, this study was conducted at a single center, namely the Kırıkkale Provincial Health Directorate, which represents a significant methodological limitation. The findings reflect the characteristics of a specific institutional context and cannot be generalized to healthcare workers employed in other provinces, institution types, or healthcare settings. Future multicenter studies involving participants from diverse geographic regions and institutional structures would provide more representative and generalizable evidence regarding BLS knowledge levels among healthcare personnel. Second, since this study employed a descriptive design with data collected at a single point in time, causal inferences between the identified factors and BLS knowledge levels cannot be drawn. Third, although the BLS training was standardized, the recency of the training was not assessed in this study. Given that knowledge retention tends to decline over time without refresher courses, the time elapsed since training may have influenced participants' knowledge scores. This should be considered a limitation and addressed in future research.

CONCLUSION

In this study, it was determined that the level of knowledge regarding BLS among employees of the Kırıkkale Provincial Health Directorate was moderate and influenced by various sociodemographic and professional factors. Although the largest proportion of participants was categorized as having high knowledge, the overall mean score of 7.12 out of 12 indicated a moderate level of knowledge when evaluated as a continuous measure. In particular, receiving BLS training, hands-on training experience, and prior experience in performing CPR were found to significantly improve both knowledge levels and self-perceived competence.

The findings indicate that not only theoretical education but also practice-based training and clinical experience play a critical role in the development of knowledge and skills. Furthermore, regularly repeated training sessions are considered essential for knowledge retention and the sustainability of skills.

Accordingly, it is recommended that periodic, practice-oriented, and guideline-based BLS training programs be implemented for all healthcare personnel, including those with limited direct patient contact. The widespread implementation of such training programs may contribute to improving emergency response capacity and, consequently, patient survival rates.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for this study was obtained from the Ethics Committee for Non-interventional Clinical Researches at Kırıkkale University (Date: 22.10.2025, Decision No: 2025.10.32).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: OK, KKK; Design: OK, KKK; Control: OK, KKK; Resources: OK, KKK; Materials: OK, KKK; Data Collection and/or Processing: OK, KKK; Analysis and/or Interpretation: OK, KKK; Literature Review: OK, KKK; Writing the Article: OK, KKK; Critical Review: OK, KKK.

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Neuroprotective effects of ascorbic acid and edaravone in experimental cerebral ischemia-reperfusion injury

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ABSTRACT

Aims: Oxidative stress-mediated ischemia-reperfusion (I/R) injury plays a critical role in secondary neuronal damage following acute ischemic stroke. This study aimed to evaluate the neuroprotective effects of edaravone and ascorbic acid administered at different doses in an experimental cerebral ischemia-reperfusion injury model.

Methods: Forty female Sprague-Dawley rats were randomly assigned using a computer-generated randomization method into five groups (n=8/group): control, low-dose edaravone (1 mg/kg), high-dose edaravone (5 mg/kg), low-dose ascorbic acid (100 mg/kg), and high-dose ascorbic acid (500 mg/kg). Experimental cerebral ischemia-reperfusion injury was induced by transient unilateral carotid artery occlusion. Treatments were administered intraperitoneally 60 minutes after ischemia induction and immediately before reperfusion. Serum malondialdehyde (MDA) and nitric oxide (NO) levels and histopathological neuronal injury were evaluated.

Results: High-dose ascorbic acid treatment was associated with significantly lower MDA, NO, and neuronal injury values compared with the control group. Serum MDA levels were significantly reduced in both low-dose and high-dose ascorbic acid groups ($p<0.05$ and $p<0.01$, respectively), whereas NO and histopathological neuronal injury values were significantly lower only in the high-dose ascorbic acid group ($p<0.05$ and $p<0.01$, respectively). Edaravone-treated groups did not demonstrate statistically significant biochemical improvement under the present experimental conditions, although mild histopathological improvement was observed.

Conclusion: In conclusion, high-dose ascorbic acid treatment was associated with reduced oxidative stress markers and decreased histopathological neuronal injury in this experimental cerebral ischemia-reperfusion model. Among the evaluated treatment protocols, high-dose ascorbic acid was associated with comparatively more favorable biochemical and histopathological findings under the present experimental conditions. However, further studies including functional neurological assessment and molecular inflammatory analyses are required to clarify the underlying mechanisms and potential translational relevance of antioxidant-based interventions in ischemic stroke.

Keywords: Ischemic stroke, cerebral ischemia-reperfusion injury, oxidative stress, neuroprotection, ascorbic acid, edaravone

INTRODUCTION

Acute ischemic stroke (AIS) remains one of the leading causes of mortality and long-term neurological disability worldwide despite substantial advances in diagnostic and therapeutic strategies.[1,3,4] Early reperfusion therapies, including thrombolytic treatment and mechanical thrombectomy, have significantly improved clinical outcomes by restoring cerebral blood flow and salvaging ischemic penumbral tissue.[3,4] However, restoration of perfusion may paradoxically induce secondary neuronal injury, known as ischemia-reperfusion (I/R) injury, which substantially contributes to infarct progression and neurological deterioration.[5,6]

The pathophysiology of cerebral I/R injury is highly complex and involves multiple interconnected molecular and cellular mechanisms, including excitotoxicity, mitochondrial dysfunction, oxidative stress, endothelial injury, inflammatory cascade activation, and apoptosis.[6,7,15-17] Among these mechanisms, oxidative stress plays a central role in the progression of neuronal damage after cerebral ischemia. During ischemia and subsequent reperfusion, excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) leads to disruption of cellular homeostasis, lipid peroxidation, protein oxidation, DNA damage, and ultimately neuronal cell death.[5-10]

Nitric oxide (NO) has dual physiological and pathological roles in cerebral ischemia. Although physiological NO

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production contributes to vascular regulation and cerebral perfusion, excessive NO generation during ischemia, particularly through neuronal NO synthase activation, promotes the formation of peroxynitrite and other cytotoxic metabolites that aggravate neuronal injury.[8,9] Peroxynitrite-mediated oxidative damage induces lipid membrane degradation and DNA oxidation, resulting in irreversible cellular injury.[9,10] Malondialdehyde (MDA), one of the major end-products of lipid peroxidation, is widely accepted as a reliable biomarker of oxidative stress and free radical-mediated tissue injury.[11-14] Therefore, evaluation of NO and MDA levels may provide important information regarding the severity of oxidative neuronal damage following cerebral ischemia-reperfusion.

Because oxidative stress is a major therapeutic target in ischemic stroke, antioxidant agents have attracted increasing attention as potential neuroprotective strategies.[7,18] Edaravone is a potent free radical scavenger with low molecular weight and lipophilic properties that enable efficient penetration through the blood-brain barrier.[18-24] Experimental studies have demonstrated that edaravone reduces oxidative stress, suppresses lipid peroxidation, preserves endothelial integrity, and attenuates inflammatory responses following cerebral ischemia.[20-24] Moreover, previous animal studies and systematic reviews have reported favorable functional and histopathological outcomes associated with edaravone treatment in focal cerebral ischemia models.[2,20,24]

Ascorbic acid (vitamin C) is another important antioxidant molecule that exerts neuroprotective effects through scavenging reactive oxygen radicals and preventing oxidative cellular injury.[25-27] As a water-soluble antioxidant, ascorbic acid contributes to the maintenance of intracellular redox balance and inhibits lipid peroxidation within the aqueous phase.[25,27] Previous experimental studies have shown that ascorbic acid administration may reduce infarct volume and neuronal injury following focal cerebral ischemia.[26,32] Nevertheless, comparative data regarding the comparative neuroprotective efficacy of edaravone and ascorbic acid in cerebral ischemia-reperfusion injury remain limited.

Therefore, the present experimental study aimed to investigate and compare the neuroprotective effects of different doses of edaravone and ascorbic acid in a rat model of acute cerebral ischemia-reperfusion injury using biochemical oxidative stress markers and histopathological neuronal injury parameters. We hypothesized that antioxidant treatment, particularly at higher doses, would attenuate oxidative stress-mediated neuronal damage and reduce histopathological injury following cerebral ischemia-reperfusion.

METHODS

Ethics

The experimental protocol was approved by the Local Ethics Committee for Animal Experiments at Kırıkkale University (Date: 21.10.2021, Decision No: 35). All procedures were conducted in accordance with the ARRIVE guidelines and the national/international guidelines for the care and use of laboratory animals.

Experimental Animals

A total of 40 adult female Sprague-Dawley rats weighing between 250 and 300 g were included in the study. Animals were housed under standardized laboratory conditions under controlled temperature and humidity with a 12-hour light/dark cycle and had free access to standard laboratory chow and water throughout the experimental period.

Inclusion and Exclusion Criteria

Healthy adult female Sprague-Dawley rats without neurological deficits or systemic disease were included in the study. Animals that developed intraoperative complications, inadequate reperfusion, anesthesia-related mortality, or technical failure during the ischemia-reperfusion procedure were excluded from the study.

Randomization and Experimental Groups

Female rats were preferred in order to reduce inter-animal physiological variability during the ischemia-reperfusion process. However, potential sex-related differences in ischemic injury response should be considered when interpreting the findings.

Animals were randomly assigned into five groups (n=8/group):

- Ischemia-reperfusion control group (C), in which carotid artery occlusion and reperfusion procedures were performed without antioxidant treatment
- Low-dose edaravone group (LDE)
- High-dose edaravone group (HDE)
- Low-dose ascorbic acid group (LDA)
- High-dose ascorbic acid group (HDA)

Histopathological analyses were performed under blinded conditions.

Experimental Cerebral Ischemia-Reperfusion Model

General anesthesia was induced using ketamine hydrochloride (90 mg/kg) and xylazine hydrochloride (10 mg/kg) administered intraperitoneally. A unilateral carotid artery occlusion model was preferred to investigate acute oxidative stress-mediated ischemia-reperfusion injury under controlled experimental conditions. Following a midline cervical incision, the left common carotid artery was carefully isolated and clamped for 90 minutes to induce ischemia. Reperfusion was subsequently established by removal of the vascular clamp. Treatments were administered 60 minutes after ischemia induction and immediately before reperfusion based on previously published experimental cerebral ischemia-reperfusion studies evaluating antioxidant administration during the pre-reperfusion period.[20,23,26] The selected edaravone and ascorbic acid doses were based on previously published experimental cerebral ischemia-reperfusion studies demonstrating antioxidant and neuroprotective efficacy.[20,23,26,32] Edaravone and ascorbic acid solutions were prepared in sterile saline and administered intraperitoneally. Equivalent volumes of sterile saline were administered intraperitoneally to the ischemia-reperfusion

control group following carotid artery occlusion and reperfusion procedures. Reperfusion was maintained for an additional 150 minutes. This reperfusion duration was selected to evaluate early oxidative stress-mediated biochemical and histopathological alterations during the acute reperfusion phase. At the end of the experimental period, blood and brain tissue samples were collected under deep anesthesia for biochemical and histopathological analyses.

Biochemical Analysis

Serum MDA and NO levels were measured using commercially available ELISA kits according to the manufacturer's instructions. MDA values were expressed as nmol/ml and NO values as µmol/L.

Histopathological Evaluation

Brain tissue samples were fixed in 10% formalin solution and embedded in paraffin blocks. Sections of 4-5 µm thickness were stained with hematoxylin-eosin and examined under light microscopy for neuronal degeneration and histopathological injury findings. Histopathological examinations were performed by a blinded histopathologist unaware of group allocation. Representative histopathological images were selected from sections demonstrating characteristic neuronal degeneration findings. Degenerative neurons characterized by eosinophilic cytoplasm, pyknotic nuclei, and loss of Nissl substance were considered atrophic neurons. Atrophic neuron percentage (ANP) was calculated by evaluating 100 pyramidal neurons at ×200 magnification in each section (**Figure**). ANP was calculated in randomly selected microscopic fields. Histopathological evaluation was performed in all animals (n=8 per group), and representative sections demonstrating characteristic neuronal degeneration findings were selected for figure preparation.

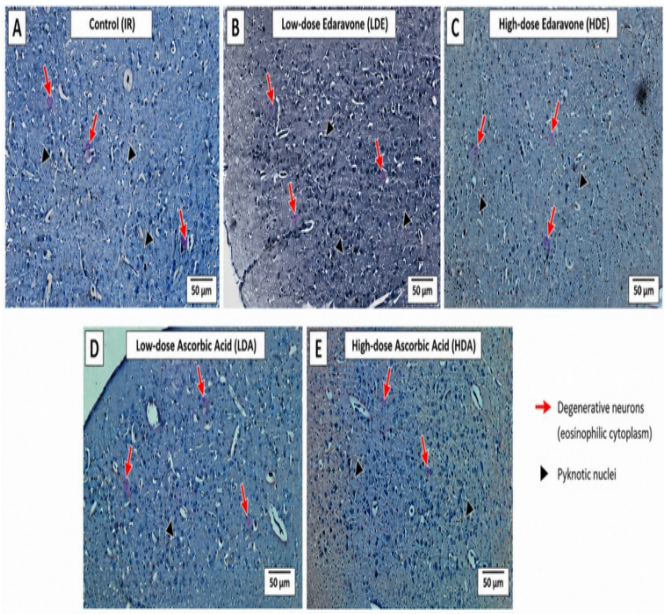

Figure. Representative histopathological findings of cerebral ischemia-reperfusion injury among experimental groups. (**A**) ischemia-reperfusion control group (C); (**B**) low-dose edaravone group (LDE); (**C**) high-dose edaravone group (HDE); (**D**) low-dose ascorbic acid group (LDA); (**E**) high-dose ascorbic acid group (HDA). Brain tissue sections were stained with hematoxylin-eosin and examined under light microscopy at ×200 magnification. Red arrows indicate degenerative neurons characterized by eosinophilic cytoplasm, whereas black arrowheads indicate pyknotic nuclei. Scale bars: 50 µm.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics version 21.0. Data were expressed as mean±standard deviation (SD). Normality distribution was assessed using the Shapiro-Wilk test. Intergroup comparisons biochemical parameters (MDA and NO) were performed using one-way analysis of variance (ANOVA) followed by Tukey post hoc analysis for pairwise subgroup comparisons. Tukey post hoc analysis was preferred for biochemical subgroup comparisons in order to control for multiple testing across normally distributed biochemical variables. Histopathological comparisons were additionally evaluated using Bonferroni correction for multiple comparisons. In response to reviewer recommendations, direct subgroup comparisons between low-dose and high-dose treatment groups were additionally analyzed using post hoc pairwise comparison tests. A p-value <0.05 was considered statistically significant. Adjusted p-values <0.0083 were considered statistically significant for Bonferroni-corrected histopathological multiple comparisons. Sample size was determined based on previously published experimental cerebral ischemia-reperfusion studies with similar biochemical and histopathological endpoints. A formal a priori power analysis was not performed because of the exploratory nature of the study. A group size of eight animals per group was considered methodologically appropriate while minimizing animal use in accordance with ethical principles and the principles of experimental animal welfare.

RESULTS

Biochemical Findings

Mean biochemical parameter values for all experimental groups are summarized in (**Table 1**). Serum MDA levels demonstrated significant differences among the experimental groups. Compared with the control group, MDA levels were significantly lower in both the low-dose ascorbic acid group (p=0.040) and the high-dose ascorbic acid group (p=0.002). No statistically significant reduction in MDA levels was observed in the edaravone-treated groups.

Table 1. Serum malondialdehyde (MDA) and nitric oxide (NO) levels among experimental groups

Group	MDA (nmol/ml) mean±SD	NO (µmol/L) mean±SD
Control	0.97±0.17	80.01±14.74
LDE	0.85±0.28	77.84±17.98
HDE	1.03±0.46	80.20±12.05
LDA	0.80±0.13*	69.18±12.96
HDA	0.71±0.10**	63.31±11.94*#

Values are presented as mean±standard deviation (SD)
Abbreviations: C: Control, SD: Standard deviation, LDE: Low-dose edaravone, HDE: High-dose edaravone, LDA: Low-dose ascorbic acid, HDA: High-dose ascorbic acid, MDA: Malondialdehyde, NO: Nitric oxide
*p<0.05 versus control, **p<0.01 versus control, #p<0.05 versus HDE group

Serum NO levels were significantly lower in the high-dose ascorbic acid group compared with the control group (p=0.026). Although lower NO levels were also observed in the low-dose ascorbic acid group, this difference did not reach statistical significance. Similarly, no statistically significant biochemical improvement was observed in the edaravone-treated groups under the present experimental conditions.

Direct Subgroup Comparisons

In response to reviewer recommendations regarding subgroup-based dose comparisons, additional direct comparisons were performed between low-dose and high-dose treatment groups. Comparisons between low-dose and high-dose edaravone groups did not demonstrate statistically significant differences in MDA or NO measurements. Similarly, direct comparison between low-dose and high-dose ascorbic acid groups did not reveal statistically significant differences for these biochemical parameters, although lower mean MDA and NO values were observed in the high-dose ascorbic acid subgroup.

Direct comparison between the high-dose edaravone and high-dose ascorbic acid groups demonstrated significantly lower NO levels in the high-dose ascorbic acid group (p=0.014). In addition, MDA values were lower in the high-dose ascorbic acid group compared with the high-dose edaravone group, although this difference did not reach statistical significance.

Histopathological Findings

Histopathological examination demonstrated varying degrees of neuronal degeneration among the experimental groups. Degenerative neurons characterized by eosinophilic cytoplasm, pyknotic nuclei, and loss of Nissl substance were predominantly observed in the control and edaravone-treated groups. The lowest neuronal injury findings were observed in the high-dose ascorbic acid group. Bonferroni-corrected multiple comparison analysis demonstrated significantly lower neuronal injury in the high-dose ascorbic acid group compared with the control group (p=0.002). Although lower neuronal injury values were also observed compared with the low-dose ascorbic acid group, this difference did not remain statistically significant after Bonferroni correction (p=0.013).

Although mild histopathological improvement was also observed in the edaravone-treated groups, these findings did not reach statistical significance after correction for multiple comparisons. Representative histopathological images are presented in **Figure**. Histopathological comparison results are summarized in **Table 2**.

Table 2. Histopathological comparison of atrophic neuron percentage (ANP) values among experimental groups

Group	ANP (%) mean±SD
Control	42.6±1.7
LDE	41.3±1.8
HDE	41.0±1.3
LDA	42.1±2.3
HDA	39.1±1.1**'

Values are presented as mean±standard deviation (SD).
Abbreviations: ANP: Atrophic neuron percentage, LDE: Low-dose edaravone, HDE: High-dose edaravone, LDA: Low-dose ascorbic acid, HDA: High-dose ascorbic acid
**p<0.01 versus control, 'p<0.0083 versus low-dose ascorbic acid group after Bonferroni correction

DISCUSSION

The present experimental study investigated the neuroprotective effects of different doses of edaravone and ascorbic acid in a rat model of cerebral ischemia-reperfusion (I/R) injury. The principal finding of the study was that high-dose ascorbic acid exerted the most prominent neuroprotective effects both biochemically and histopathologically. High-dose ascorbic acid significantly reduced serum MDA and NO levels and attenuated neuronal degeneration compared with the control group. In contrast, edaravone treatment did not produce statistically significant biochemical improvements under the conditions of the present experimental model. Among the evaluated treatment protocols, high-dose ascorbic acid was associated with comparatively more favorable biochemical and histopathological findings under the present experimental conditions.

AIS initiates a complex pathophysiological cascade involving excitotoxicity, oxidative stress, inflammatory activation, endothelial dysfunction, mitochondrial injury, and apoptosis.[5-7,15-17] Although reperfusion therapies are essential for restoring cerebral blood flow and salvaging ischemic penumbral tissue, reperfusion itself may paradoxically aggravate neuronal injury through excessive production of ROS and RNS.[5-7] Oxidative stress therefore remains one of the major mechanisms contributing to secondary neuronal injury after ischemic stroke.

In the present study, serum MDA levels were significantly reduced in both low-dose and high-dose ascorbic acid groups compared with the control group. MDA is a well-established marker of lipid peroxidation and oxidative tissue injury.[11-14] Elevated MDA levels reflect free radical-mediated membrane degradation and neuronal cellular injury. Therefore, the reduction in MDA levels observed after ascorbic acid treatment suggests attenuation of oxidative membrane damage during cerebral ischemia-reperfusion injury. These findings are consistent with previous experimental studies demonstrating antioxidant and neuroprotective properties of ascorbic acid in ischemic brain injury models.[26,27,32]

NO has both physiological and pathological roles in cerebral ischemia. Excessive NO production during ischemia contributes to formation of peroxynitrite and other cytotoxic metabolites that promote mitochondrial dysfunction, DNA oxidation, and neuronal apoptosis.[8-10] In the present study, high-dose ascorbic acid significantly reduced NO levels compared with the control group, indicating suppression of nitrosative stress pathways. The concurrent reduction of both MDA and NO levels strongly supports the hypothesis that antioxidant therapy attenuates oxidative neuronal injury following cerebral ischemia-reperfusion. However, direct subgroup comparisons between low-dose and high-dose ascorbic acid groups did not demonstrate statistically significant differences for MDA and NO measurements, although lower mean values were observed in the high-dose subgroup. Therefore, the present findings should not be interpreted as definitive evidence of a dose-dependent neuroprotective effect.

Histopathological findings further supported the biochemical results. The lowest ANP was observed in the high-dose ascorbic acid group, indicating reduced neuronal degeneration after ischemia-reperfusion injury. Degenerative neuronal changes, including eosinophilic cytoplasm, pyknotic nuclei, and loss of Nissl substance, were

substantially less prominent in the high-dose ascorbic acid group. Furthermore, lower ANP values observed in the high-dose compared with the low-dose ascorbic acid group suggest comparatively greater histopathological improvement in the high-dose ascorbic acid subgroup. Bonferroni-corrected multiple comparison analysis demonstrated significantly lower neuronal injury findings in the high-dose ascorbic acid group compared with the control group. Although lower neuronal injury values were also observed compared with the low-dose ascorbic acid group, this difference did not remain statistically significant after Bonferroni correction (p=0.013). These histopathological findings support the biochemical results and suggest that attenuation of oxidative stress may contribute to reduced neuronal degeneration following reperfusion injury.

Ascorbic acid is a potent water-soluble antioxidant capable of scavenging free radicals within intracellular and extracellular compartments.[25,27] In addition to its antioxidant activity, ascorbic acid contributes to preservation of endothelial integrity and modulation of inflammatory pathways. Previous studies demonstrated reduced infarct volume and attenuation of neuronal injury following ascorbic acid administration in focal cerebral ischemia models.[26,32] The present findings further support the potential neuroprotective role of high-dose ascorbic acid in ischemia-reperfusion injury. In addition, alternative antioxidant strategies involving dehydroascorbic acid have also been proposed because of improved blood-brain barrier transport characteristics.[31] Experimental antioxidant pretreatment studies have similarly demonstrated attenuation of ischemic neuronal injury.[33,34]

Edaravone is another established free radical scavenger that has demonstrated neuroprotective efficacy in both experimental and clinical studies.[18-24,28] Previous reports showed that edaravone suppresses oxidative tissue injury, inflammatory responses, and endothelial dysfunction following cerebral ischemia.[20-24] Oishi et al.[29] demonstrated attenuation of ischemia-induced metabolic alterations with edaravone treatment, while Zhang et al.[30] reported reduced oxidative injury in myocardial reperfusion models. However, unlike previous reports, statistically significant biochemical improvements were not observed in edaravone-treated groups in the present study.

Several factors may explain these findings. The neuroprotective efficacy of edaravone may be highly dependent on timing of administration, ischemia duration, and tissue bioavailability.[2,23] Variability in experimental protocols may substantially influence treatment efficacy. Additionally, ischemia-reperfusion injury involves multiple overlapping molecular pathways beyond oxidative stress alone, and suppression of free radical production may be insufficient to completely prevent neuronal injury under certain conditions. Several methodological and experimental factors may therefore have contributed to the relatively limited biochemical response observed in the present study, including treatment timing, reperfusion duration, dose selection, and characteristics of the selected ischemia-reperfusion model.

Interestingly, although edaravone-treated groups did not demonstrate statistically significant biochemical improvements, histopathological neuronal degeneration appeared slightly reduced compared with the control group. This discrepancy may indicate partial local neuroprotective effects that were not fully reflected by serum oxidative stress markers alone. Interestingly, the HDE group demonstrated numerically higher MDA levels compared with the ischemia-reperfusion control group, although this difference did not reach statistical significance. The relatively high standard deviation observed in the HDE group may reflect biological variability within the experimental model and may have contributed to the absence of statistically significant biochemical improvement.

In response to reviewer recommendations, direct subgroup comparisons were additionally performed between low-dose and high-dose treatment groups. Comparisons between low-dose and high-dose edaravone groups did not demonstrate statistically significant differences in MDA or NO measurements. Direct comparison between the high-dose edaravone and high-dose ascorbic acid groups demonstrated significantly lower NO levels in the high-dose ascorbic acid group.

The translational implications of the present findings are clinically important. Despite advances in thrombolytic therapy and mechanical thrombectomy, ischemia-reperfusion injury remains a major contributor to secondary neuronal damage after AIS.[3,4] Antioxidant therapies targeting oxidative stress pathways may therefore provide additional therapeutic benefit following successful reperfusion. Antioxidant supplementation has also demonstrated protective effects in extracerebral ischemia-reperfusion models, including myocardial reperfusion injury and cardiac surgery.[30,35]

Although middle cerebral artery occlusion (MCAO) remains one of the most widely used and accepted experimental models for focal cerebral ischemia, recent reviews emphasize that different animal models may be selected according to the specific mechanistic endpoint being investigated, including oxidative stress, reperfusion-related biochemical alterations, and early neuronal injury. The unilateral carotid artery occlusion model used in the present study provided a reproducible experimental environment for evaluating acute oxidative stress-mediated ischemia-reperfusion injury and early biochemical alterations under controlled conditions. Nevertheless, consistent with recent discussions on the limitations of experimental stroke models, this model may not fully reproduce the complex vascular, thromboembolic, and pathophysiological characteristics of human focal ischemic stroke.[36,37]

Overall, the present findings suggest that high-dose ascorbic acid was associated with significant biochemical and histopathological improvement following cerebral ischemia-reperfusion injury. Recent literature continues to support oxidative stress as a central mechanism in cerebral ischemia-reperfusion injury and highlights antioxidant-based neuroprotective strategies as an active area of experimental stroke research. However, although direct subgroup comparisons were additionally performed in response to reviewer recommendations, the present study was not primarily designed or statistically powered to establish a

definitive dose-response relationship between antioxidant treatment intensity and neuroprotective efficacy. Therefore, further studies incorporating functional neurological assessment, molecular inflammatory/apoptotic markers, infarct volume analysis, and larger experimental cohorts are required to clarify the mechanisms and translational relevance of antioxidant-based neuroprotective strategies in ischemic stroke.[38,39]

Limitations

Several limitations of the present study should be acknowledged. Infarct volume measurements, cerebral edema evaluation, and brain weight analysis were not performed. In addition, advanced immunohistochemical analyses, including apoptotic and inflammatory markers such as caspase-3, TUNEL, GFAP, and Iba-1 were not evaluated. Therefore, the molecular and mechanistic basis of the observed neuroprotective findings could not be fully clarified. The relatively short reperfusion period may not fully reflect delayed neuronal injury and long-term neuroinflammatory processes observed in clinical stroke. Therefore, delayed apoptotic and inflammatory responses occurring during later reperfusion stages could not be comprehensively evaluated in the present study. In addition, functional neurological assessment tools, including Bederson and Garcia neurological deficit scores, were not evaluated in the present study. Therefore, the translational and clinical relevance of the observed neuroprotective findings could not be fully determined. Furthermore, although the experimental model reproduced important aspects of oxidative neuronal injury, it may not completely represent the complex pathophysiology of human AIS. In addition, a separate sham-operated group was not included in the present experimental design. Therefore, the isolated effects of anesthesia, surgical manipulation, and vascular exposure could not be evaluated independently from ischemia-reperfusion injury.

CONCLUSION

As a result, the present study demonstrated that high-dose ascorbic acid was associated with significant biochemical and histopathological improvement against cerebral ischemia-reperfusion injury. Reduction of oxidative stress markers and attenuation of neuronal degeneration suggest that high-dose antioxidant therapy may represent a promising strategy for limiting secondary neuronal injury after AIS. Further translational studies are warranted to determine the optimal therapeutic timing, dosage, and clinical applicability of antioxidant agents in ischemic stroke management.

ETHICAL DECLARATIONS

Ethics Committee Approval

The experimental protocol was approved by the Local Ethics Committee for Animal Experiments at Kırıkkale University (Date: 21.10.2021, Decision No: 35).

Informed Consent

Since this study involved animal experimentation, informed consent was not required.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Conceptualization: PB, OE; Methodology: PB, OE, YŞ; Data Collection: PB, EC, MZ, ÜK; Formal Analysis: PB; Writing–Original Draft: PB; Writing–Review and Editing: OE, TD.

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Case Report

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Surgical strategy to prevent moderate patient–prosthesis mismatch in infective endocarditis complicated by a narrow aortic root: a case report

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ABSTRACT

A 65-year-old male presented with fever, progressive dyspnea, bilateral lower-extremity edema, and new-onset angina. Transesophageal echocardiography and coronary computed tomography angiography revealed severe aortic and tricuspid regurgitation with large vegetations, moderate mitral regurgitation, a narrow aortic root, and critical stenoses of the left main and right coronary arteries. Blood cultures grew vancomycin-sensitive *Enterococcus faecalis*. The patient underwent urgent aortic and tricuspid valve replacement, mitral valve repair, and triple-vessel coronary artery bypass grafting. Because of the narrow aortic root, the Nicks procedure was performed to provide adequate prosthetic valve area and to prevent patient–prosthesis mismatch (PPM). This rare adult case emphasizes the importance of preoperative indexed effective orifice area (iEOA) calculations and highlights the role of Nicks, Manouguian, and Yang enlargement techniques in preventing PPM and managing complex left ventricular outflow tract pathology.

Keywords: Infective endocarditis, aortic root enlargement, patient–prosthesis mismatch, indexed effective orifice area, Nicks procedure

INTRODUCTION

Despite advancements in antimicrobial therapy, *Enterococcus faecalis* infective endocarditis remains a significant clinical challenge, with mortality rates between 20% and 40%, and surgical intervention required in approximately 40% of cases, distinguishing it from other endocarditis etiologies.[1] Surgical indications in infective endocarditis include severe valvular stenosis or regurgitation unresponsive to medical therapy, uncontrolled intracardiac abscess, pseudoaneurysm, fistula, rapidly enlarging vegetation, vegetation exceeding 10 mm with recurrent embolism, vegetation larger than 15 mm irrespective of embolic events, refractory pulmonary edema, or cardiogenic shock.[1] In prosthetic valve infective endocarditis, indications differ slightly, encompassing recurrent blood transfusions due to hemolysis from paravalvular leak (PVL), new or worsening New York Heart Association (NYHA) class III-IV heart failure symptoms, endocarditis-related PVL, elevated pulmonary artery pressures with left atrial dilation, and scenarios where medical management proves inadequate; rocking motion exceeding 15 degrees, indicative of annular dehiscence, necessitates urgent surgery to prevent hemodynamic collapse.[2] In patients with a small aortic annulus, the clinical benefits of aortic valve replacement depend on the prevention of PPM. This technique is useful for enabling the implantation of larger prosthetic valves to avoid such mismatch.[3] This report presents a rare adult case of infective endocarditis complicated by a narrow aortic root requiring complex multivalve intervention in which the Nicks procedure was performed to prevent PPM.

CASE

A 65-year-old male (172 cm, 75 kg) presented with fever, fatigue, bilateral leg edema, and exertional dyspnea (NYHA II–III). His past medical history included chronic obstructive pulmonary disease, hypertension, and atrial fibrillation. Laboratory evaluation confirmed elevated inflammatory markers, and blood cultures yielded vancomycin-sensitive *Enterococcus faecalis*. Transesophageal echocardiography showed an ejection fraction of 40-45%, a narrow aortic root, a 5x8 mm mobile vegetation on the aortic valve, a 19x10 mm vegetation on the tricuspid valve, and mild mitral valve destruction (**Figure 1A**). Coronary computed tomography (CT) angiography was performed due to acute chest pain and rising troponin levels. Critical stenoses were identified in both the left main coronary artery and proximal right coronary artery (**Figure 1B, C**). Given the severity of valvular destruction, large vegetations, multivessel coronary disease, and the patient's clinical deterioration, urgent surgery was scheduled.

Surgical Procedure

Following median sternotomy, arterial cannulation was achieved via the aorta, with venous cannulation through the superior and inferior vena cavae. Cardiopulmonary bypass (CPB) was initiated. After aortic cross-clamping, antegrade Del Nido cardioplegia induced cardiac arrest. To minimize embolization risk from vegetation, superior and inferior vena cava snares were tightened post-cross-clamping, and a vent cannula was placed in the right superior pulmonary vein;

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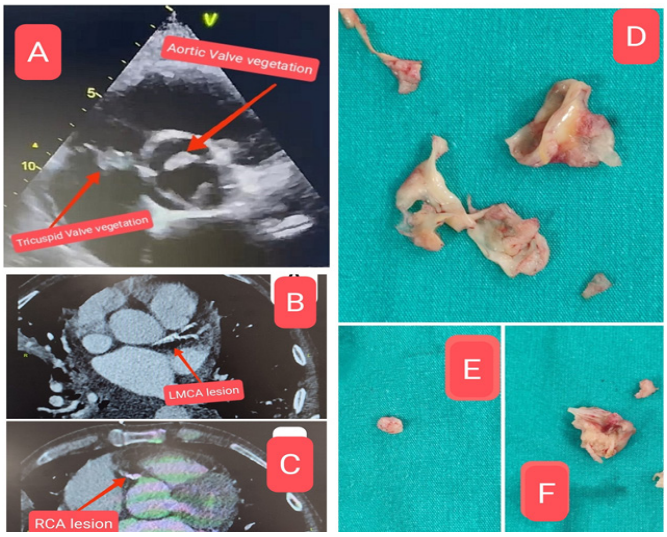

Figure 1. Preoperative echocardiographic and coronary computed tomography angiographic findings, and intraoperative images of the resected aortic, mitral, and tricuspid valves with vegetations.
A) Echocardiographic images demonstrating vegetations on the aortic and tricuspid valves.
B) Coronary computed tomography angiographic view showing an atherosclerotic lesion causing stenosis in the left main coronary artery.
C) Coronary computed tomography angiographic view showing an atherosclerotic lesion causing stenosis in the right coronary artery.
D) Intraoperative image of the resected aortic valve and vegetations.
E) Image of the resected mitral valve and associated vegetation.
F) Image of the resected tricuspid valve and vegetations.

cardiac manipulation was avoided prior to clamping. Distal anastomoses for left anterior descending (LAD), circumflex (CX), and right coronary artery (RCA) were completed using saphenous vein grafts. The mitral valve was accessed via a transseptal approach, with destruction at the anterolateral commissure repaired using pledgeted sutures. The tricuspid valve and its vegetation were excised, followed by biological valve replacement (Epic, No. 33, USA). The aortic valve and vegetation were then excised, with biological valve replacement (Epic, No. 23, USA) (**Figure 1D, F**).

Because intraoperative sizing revealed a 21-mm aortic annulus—insufficient to accommodate the required prosthesis without generating PPM—the Nicks procedure was performed. The aortotomy was extended through the midpoint of the non-coronary sinus into the aortomitral curtain. A bovine pericardial patch was used to enlarge the root, enabling safe implantation of the larger prosthetic valve. Proximal coronary anastomoses were completed, the cross-clamp was removed, and the patient was weaned off CPB uneventfully. Postoperative recovery was stable. After completing a six-week parenteral antibiotic course, the patient was discharged without complications.

DISCUSSION

In cases involving intracardiac space-occupying lesions—such as tumors, abscesses, hematomas, or vegetations resulting from infective endocarditis—we employ a 'no-touch' surgical strategy prior to aortic cross-clamping to minimize the risk of intraoperative embolization.[4] In patients at risk for PPM, posterior aortic root enlargement can be achieved using the Nicks, Manouguian, or Yang procedures, whereas a more extensive enlargement—albeit with increased operative risk—can be accomplished through the anterior enlargement technique known as the Konno–Rastan procedure (**Figure 2A**). The Nicks procedure involves an incision from the midpoint of the non-coronary sinus through the aortic annulus into the aortomitral fibrous curtain, typically without extending to the mitral anterior leaflet, followed by patch repair using pericardium or Dacron to enlarge the annulus, allowing implantation of a one-size larger prosthetic valve (**Figure 2B**).[5] In this case, the procedure facilitated larger valve replacement, prevented PPM, and created space for future transcatheter aortic valve implantation (valve-in-valve) procedures.[5] The Manouguian technique involves extending the incision from the commissure between the noncoronary and left coronary cusps toward the anterior leaflet of the mitral valve. In addition, the technique requires opening the roof of the left atrium. Although it provides greater enlargement of the aortic root, this procedure carries a risk of inducing mitral regurgitation. This procedure typically permits implantation of a prosthetic valve that is two to three sizes larger. In the Yang procedure, the incision begins at the commissure between the noncoronary and left coronary cusps and is extended toward the aortomitral curtain in an inverted 'Y' configuration. The resulting defect is repaired using a rectangular patch. This technique does not cause mitral regurgitation and allows implantation of larger prosthetic valves compared with the Manouguian technique; however, because it does not enlarge the basal ring of the aortic root, it is not preferred in cases of subvalvular stenosis. Although the Yang procedure facilitates the implantation of larger prostheses, it may make closure of the aortotomy more challenging. Furthermore, reconstruction of the aortic annulus with a rectangular patch may rotate or distort the left coronary ostium, thereby increasing the risk of coronary obstruction. Finally, deformation of the prosthetic valve during implantation may predispose it to structural deterioration and result in turbulent periprosthetic flow. This procedure generally allows implantation of a prosthetic valve that is three to five sizes larger.[5] Hemodynamic turbulence generated by a deformed prosthetic aortic valve may, over time, contribute to the formation of an acquired discrete subaortic membrane.[6] The Konno–Rastan procedure (anterior aortoventriculoplasty) can achieve a 40-50% enlargement of the aortic root. This procedure is an effective method for relieving subvalvular, valvular, or supravalvular left ventricular outflow tract obstruction. However, due to the complexity of the surrounding anatomical structures, the technique is technically demanding. Reported complications include septal artery injury, iatrogenic damage to the pulmonary valve, prosthetic valve dysfunction, infective endocarditis, complete atrioventricular block requiring permanent pacemaker implantation, RCA injury, and prolonged CPB times.

According to literature, iEOA is defined as the ratio of effective orifice area (EOA) to body surface area (BSA). Guidelines recommend a target iEOA greater than 0.85 cm^2/m^2 to avoid PPM, with moderate PPM occurring at 0.65–0.85 cm^2/m^2 and severe PPM at ≤0.65 cm^2/m^2.[7] To prevent PPM:

- Calculate target EOA by multiplying target iEOA (0.85 cm^2/m^2) by BSA;
- Select prosthesis from published model-specific EOA tables;

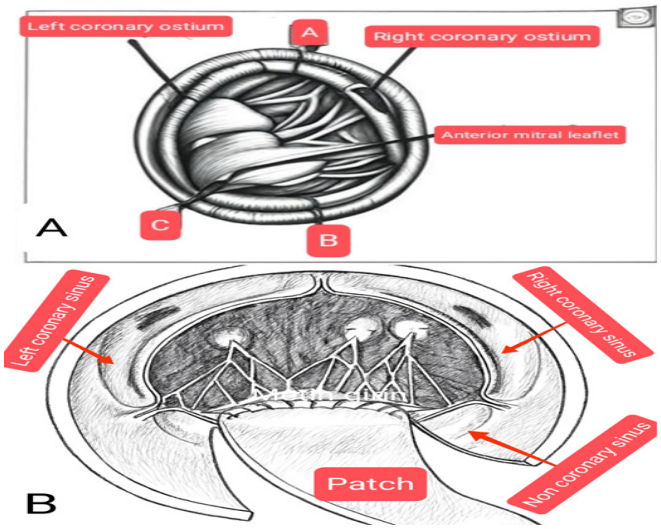

Figure 2. Surgical anatomy of the aortic root after leaflet excision and schematic illustration of the patch placement technique used in the Nicks procedure.
2A. **Point A:** In the Konno–Rastan procedure, the incision extends through the right coronary cusp, across the aortic annulus, and into the interventricular septum.
Point B: In the Nicks procedure, the incision is made through the midpoint of the non-coronary cusp and extended toward the aortomitral fibrosa.
Point C: When the incision is extended from the commissure between the non-coronary and left coronary cusps toward the anterior mitral leaflet, it represents the Manouguian technique; If the incision is extended in an inverted Y configuration that undermines both cusps, it corresponds to the starting point of the Yang procedure.
2B. Schematic illustration of patch placement along the incision performed through the midpoint of the non-coronary cusp during the Nicks procedure.

- Compare prosthesis EOA to target—if prosthesis EOA ≥ target, proceed; if < target, opt for larger valve or root enlargement;

- Compare intraoperative annulus diameter to prosthesis—if equivalent, implant; if 2-3 mm smaller, consider Nicks for one-size enlargement; if 4-6 mm smaller, Yang or Manouguian for 1.5-2 sizes; If it is at least 6-8 mm smaller, consider a Konno-Rastan procedure or aortic root replacement;

- Re-measure post-enlargement annulus with sizers before implantation. Some valve designs provide larger EOA values for the same labeled valve size, and tables presenting published EOA data are available in the literature.

In the presented case, BSA was approximately 1.89 m^2. To avert PPM, the target EOA for the prosthetic valve was ≥1.61 cm^2 (0.85 $cm^2/m^2 \times 1.89\ m^2 \approx 1.61\ cm^2$). Based on manufacturer-specific EOA tables, this required a minimum 23-mm prosthesis. Intraoperative annulus measured 21 mm with sizers. The 2-3 mm discrepancy between target and actual size prompted Nicks procedure for one-size enlargement. Postoperative echocardiographic follow-up confirmed that the cardiac valves were functional and that no PPM had developed at the aortic valve.

To our knowledge, this is one of the very few reported adult cases of multivalvular infective endocarditis combined with critical left main and right coronary artery disease in which an iEOA–guided algorithm was prospectively applied to determine the need for posterior aortic root enlargement.

CONCLUSION

This case underscores the importance of meticulous preoperative evaluation—including iEOA-guided planning—in the management of complex infective endocarditis with a narrow aortic root. It also highlights the critical role of surgical strategy in patients with a narrow aortic root who are predisposed to developing PPM. Aortic root enlargement remains an essential tool in the surgical armamentarium for selected high-risk patients requiring aortic valve replacement.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient(s) included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

Concept: NAB, NK, TT, MC, DD; Design: NAB, NK, TT, MC, DD; Control: NAB, NK, TT, MC, DD; Resources: NAB, NK, TT, MC, DD; Materials: NAB, NK, TT, MC, DD; Data Collection and/or Processing: NAB, NK, TT, MC, DD; Analysis and/or Interpretation: NAB, NK, TT, MC, DD; Literature Review: NAB, NK, TT, MC, DD; Writing the Article: NAB, NK, TT, MC, DD; Critical Review: NAB, NK, TT, MC, DD.

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Letter to the Editor

COVID-19 and cardiocerebral infarction: anecdotal or empiric link?—A call for rigorous data

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Dear Editor,

We write to bring to cognisance, an incipient but interesting concern in interdisciplinary brain and cardiovascular science.

Cardiocerebral infarction (CCI), the simultaneous (defined as occurring within 24 hours of each other) or sequential occurrence of acute myocardial infarction (AMI) and acute ischemic stroke (AIS), is a rare, multifactorial but highly lethal condition.[1] In a recent Singapore registry of over 120,000 patients with AMI or AIS, only 0.5% had synchronous CCI and 0.8% metachronous CCI.[2] Nevertheless, CCI carries far higher 30-day mortality than isolated AMI or stroke.[2] By definition, then, any condition that increases the risk of both stroke and myocardial infarction could plausibly precipitate CCI. SARS-CoV-2 infection (COVID-19) has been associated with both stroke and AMI, suggesting a potential role in CCI that merits urgent attention.[1,2]

COVID-19, Hypercoagulability and Vascular Risk

COVID-19 is now known to trigger a systemic pro-thrombotic state. Large-scale epidemiologic studies have demonstrated that patients with COVID-19 face a markedly elevated risk of cardiovascular events. For example, a population-based cohort in Sweden found that, in the first two weeks after COVID-19, the odds of AMI were ~3.4-fold and of ischemic stroke ~3.6-fold higher compared to matched controls.[3] Similarly, hospitalized COVID-19 patients have higher stroke rates than those with influenza.[4] A recent meta-analysis of 155 studies reported that individuals are roughly three times more likely to suffer a heart attack and three times more likely to suffer a stroke in the 14 weeks following COVID-19 infection.[5] These startling figures underline that COVID-19 substantially heightens both cardiac and neurologic vascular risk.

Functionally, SARS-CoV-2 induces widespread endothelial injury and inflammation. Post-mortem studies have shown viral invasion of endothelium, lymphocytic endothelitis, and diffuse microvascular thrombosis in multiple organs.[6] Inflammatory cytokine release and neutrophil extracellular traps can sustain a hypercoagulable nidus even after acute infection.[6,7] In one conceptual model, COVID-19–triggered endothelial dysfunction creates a vicious cycle of arterial inflammation, platelet activation, and impaired fibrinolysis, predisposing to both macro- and microvascular thromboses.[6,7] Thus, SARS-CoV-2 infection can in theory promote simultaneous or near-simultaneous arterial occlusions in the coronary and cerebral circulations.

Key proposed mechanisms linking COVID-19 to CCI include:

- **Endothelial damage:** SARS-CoV-2 infects endothelial cells via Angiotensin converting enzyme 2 (ACE2), causing dysfunction and a switch to a prothrombotic state.[6]
- **Hyperinflammation and coagulopathy:** Persistent cytokines (e.g. IL-6, TNF-α) and procoagulant factors (e.g. von Willebrand factor, NETs) promote clot formation in arteries.[6]
- **Plaque destabilization:** Systemic inflammation may destabilize atherosclerotic plaques, triggering plaque rupture in both carotid/cerebral and coronary arteries simultaneously although this is speculative.
- **Cardiac effects:** Myocardial injury or dysfunction from COVID-19 could itself generate ventricular thrombi or arrhythmias leading to stroke via embolism.[7]

Despite plausible biology, direct evidence linking CCI with COVID-19 is largely anecdotal. An important unresolved distinction is whether COVID-19 acts as a primary cause of CCI, an accelerant of pre-existing vascular instability, or merely an unmasker through heightened surveillance and hospitalization. Disentangling these roles is essential, as each carries different implications for prevention and anticoagulation strategies. The literature consists mostly of case reports and small series. A study reported five COVID-19–era patients presenting with simultaneous AMI

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and AIS within one month.[8] These patients required complex care (thrombolysis withheld, anticoagulation managed carefully) and suffered high morbidity/mortality. In their brief series, the authors hypothesized that inflammatory and immunological endothelial systemic damage from COVID-19 might underlie the phenomenon.[9] A 2023 systematic review identified only 12 published cases of cardio-cerebral infarction in COVID-19 patients.[10] Two-thirds of these had truly simultaneous events; most were middle-aged men with vascular risk factors. Outcomes were uniformly poor (70% had lasting deficits; 1/10 died in that small cohort) (**Figure**).[10]

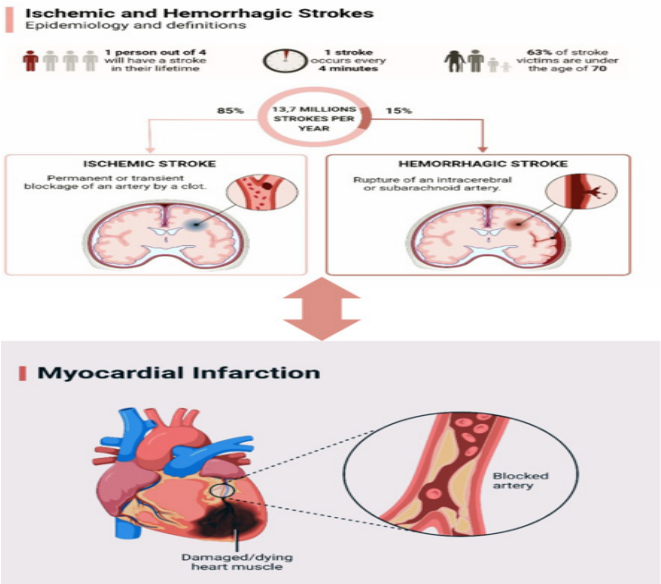

Figure. Schematic representation of the proposed pathophysiological mechanisms by which SARS-CoV-2 infection may lead to concurrent acute myocardial infarction and acute ischemic stroke (cardiocerebral infarction, CCI). Key pathways depicted include endothelial dysfunction, hypercoagulability, cytokine-mediated inflammation, and plaque destabilization.[1-10]

The Data Gap: Lack of Epidemiology and Autopsy Series

To date there are no large epidemiological studies or meta-analyses explicitly quantifying COVID-19–associated CCI. Aside from isolated case descriptions, the incidence of CCI in COVID-19 is unknown. Existing stroke or AMI registries rarely capture dual infarctions, and published data come from heterogeneous sources (case series, narrative reviews, or overlapping cohorts). In the Singapore national registries, for example, only pre-pandemic and early-pandemic AMI/stroke cases have been analyzed for CCI incidence;[2] no subgroup analysis on COVID-19 patients was reported. Likewise, meta-analyses of COVID-19 complications have focused on stroke or AMI separately, not on combined events.

Postmortem studies could potentially reveal undiagnosed CCI, but published autopsy series have not systematically reported concomitant brain and heart infarctions. Most COVID-19 autopsies describe diffuse microthrombi, pulmonary emboli, myocarditis, and small strokes,[6] but seldom focus on large-vessel infarctions in multiple organs. With only scattered reports (and in many regions few autopsies at all), it is impossible to know whether some fatalities were due to unrecognized CCI. Thus there exists a glaring paucity of data – no population-level risk estimates, no unified case definitions, and almost no pathological documentation of COVID-related CCI. Therefore, a connection has been suggested but there is currently limited evidence and more studies are needed.

A further reason why CCI data remain scarce is diagnostic masking. In patients with severe COVID-19 or those suffering profound neurological deficits from an AIS, the cardinal symptoms of AMI—chest pain, dyspnea, and haemodynamic compromise—may be obscured by the dominant clinical presentation. Conversely, altered consciousness or sedation may prevent patients from reporting ischaemic chest discomfort. This bidirectional masking likely leads to systematic under-ascertainment of dual events in routine clinical practice and in existing registries. To mitigate this, we advocate for standardised screening protocols in which all acute stroke patients with confirmed or suspected COVID-19 receive serial troponin measurements and a 12-lead electrocardiogram at presentation and at 6 and 24 hours; reciprocally, COVID-19 patients admitted with AMI should undergo neurological assessment and, where feasible, brain imaging. Such protocols would not only improve individual patient care but would generate the denominator data required for reliable epidemiological estimates of CCI incidence. Additionally, to determine whether COVID-19 acts as a de novo trigger for CCI rather than merely an accelerant of pre-existing vascular disease, future studies must stratify patients by baseline vascular risk. The available anecdotal reports predominantly describe middle-aged men with established vascular risk factors; it remains unclear whether CCI can occur in younger, low-risk individuals without underlying atherosclerosis. Demonstrating CCI in such populations would provide stronger evidence that SARS-CoV-2 is capable of precipitating multi-territory arterial thrombosis independently of pre-existing disease, with important implications for primary prevention during future coronavirus outbreaks.

Implications and Recommendations

The potential for COVID-19 to trigger CCI has serious clinical implications. Neurologists and cardiologists must be alert to the possibility of dual events, as management (thrombolysis, anticoagulation, intervention) can be complex. For researchers, this gap highlights an urgent need. Possible steps include:

- **Epidemiologic surveillance:** Leverage large electronic health databases to identify patients with both stroke and AMI diagnoses within a short window of COVID-19 infection. International registries (e.g, biobanks, national cardiology databases) should consider extracting CCI events.
- **Case series and cohorts:** Prospective cohorts of hospitalized COVID-19 patients should report any simultaneous stroke and AMI. A standard definition (e.g. within 24 hours vs 1 week) would aid comparability.
- **Autopsy studies:** Pathologists should document and report findings of macrovascular infarction in both brain and heart in fatal COVID-19 cases. Systematic complete autopsies (brain and heart examined) could reveal silent infarcts.
- **Meta-analyses:** A collaborative meta-analysis of reported cases could pool data on demographics, timing, and outcomes to generate hypotheses.

At present, our knowledge rests on logic and sparse case data: COVID-19 certainly raises stroke and MI risk individually,[3,4] and it is biochemically plausible it could cause both together. But calling COVID-19 a definitive cause of CCI would be premature without systematic evidence. We reverberate calls from experts that rigorous data collection is needed before drawing firm conclusions.[8,10] Only then can we understand how often COVID-19 alongside other implicated factors, precipitate CCI, which patients are most at risk, and how best to prevent or treat this devastating syndrome.

ETHICAL DECLARATIONS

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