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RESEARCH ARTICLE

The Relationship between Microsatellite Instability and KRAS Mutations in Liver-metastatic Colorectal Cancer: A Preliminary Cross-sectional Study

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Abstract

Background: Colorectal cancer (CRC) has a high mortality rate due to the development of liver metastases. Mutations in RAS and mismatch repair (MMR) genes are common in CRC, with Kirsten rat sarcoma viral oncogene (KRAS) mutations occurring in approximately 44% of cases and MSI in 15%. Both mutations are associated with poor prognosis. The study aims to identify MSI status and KRAS mutations in liver-metastatic CRC at a hospital in eastern Indonesia. **Methods:** In this cross-sectional study, 57 patients with liver-metastatic CRC were included. We evaluated KRAS mutations and microsatellite instability (MSI) status in patients' DNA extracted from paraffin blocks. The procedures involved included specimen examination, DNA extraction, and genetic sequencing. The data were analyzed using SPSS version 25.0. Fisher's exact test was utilized to evaluate the relationship between MSI status and KRAS mutations. A significance level of $p<0.05$ was considered statistically significant. **Results:** This study included patients aged 16–80 years with liver-metastatic colon cancer. Patients were primarily male with left-sided tumors of adenocarcinomatous histopathology and high histopathological grade. Of the 57 subjects, 31.6% had MSI-high (MSI-H) tumors and 21.1% expressed mutant KRAS. The majority of MSI-H tumors (82% of patients) expressed mutant KRAS, while most MSI-low (MSI-L) tumors (60% of patients) expressed wild-type KRAS. However, Fisher's exact test indicated no significant relationship between MSI status and KRAS mutation status in liver-metastatic colon cancer ($p = 0.489$). **Conclusions:** This study found no significant relationship between MSI status and KRAS mutation status in patients with liver-metastatic colon cancer.

Keywords: KRAS protein- colorectal cancer- DNA mismatch repair- liver- neoplasm- metastasis

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Introduction

The high mortality rate of colorectal cancer (CRC) is generally caused by the development of metastasis during the course of the disease [1, 2]; the liver is a frequent target organ for metastatic spread [3]. Approximately 25% of CRC patients have hepatic metastases at the time of diagnosis, and about 50% of CRC patients will develop liver-metastatic lesions during the course of their disease [4, 5]. If left untreated, patients with liver-metastatic CRC have a median survival of only six to nine months [6].

Mutations in Rat Sarcoma Viral Oncogene Homolog (RAS) and mismatch repair (MMR) genes are the most commonly observed prognostic markers in CRC. Among RAS mutations, Kirsten rat sarcoma viral oncogene (KRAS) mutations (85%) are the most frequently found, followed by neuroblastoma ras viral oncogene homolog (15%) and Harvey Rat sarcoma viral oncogene homolog HRAS (1%). KRAS mutations occur in approximately 44% of CRC cases; the majority of mutations are located

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in codons 12 and 13 of exon 2 (80% are G12D, G12V, G12C, G12A, or G13D mutations) [7]. MMR gene mutations or microsatellite instability (MSI) are found in 15% of CRC patients, 12% of which are sporadic CRC cases (the remaining 3% are nonpolyposis hereditary CRC cases) [8]. Meta-analyses have reported that KRAS mutations are found in 25–52% of patients with liver-metastatic colon cancer. Most studies report that KRAS mutations are negative prognostic factors for overall and disease-free survival [9]. KRAS mutations are known to be associated with increased heat shock protein expression and activation of PI3K/mTORC2-dependent AKT, thus enhancing cancer cell survival in the liver [10]. MSI-high (MSI-H) tumors are identified in approximately 15% of CRC patients. Deficiencies in DNA mismatch repair protein such MutS homolog 2, MutL protein homolog 1, and mutS homolog 6 protein production can result in impaired mismatch base detection, leading to the expression of abnormal proteins that can be recognized as neoantigens by the immune system. Additionally, this deficiency causes apoptosis to fail after DNA damage is detected. The MMR-deficient/MSI-H phenotype has been associated with the inefficacy of fluoropyrimidine therapy in patients with stage II or III CRC [11]. Interestingly, the proportion of MSI-H tumors among patients with liver-metastatic colon cancer has not been reported to date.

The ability to identify genomic variants has revolutionized clinicians' understanding of how cancer develops. Molecular cancer biomarkers are indicators that can be detected in every patient and can help estimate cancer risk, cancer incidence, patient prognosis, and response to therapy. Our institution is a central referral hospital in eastern Indonesia, where no previous research has been conducted to determine MSI status and identify KRAS mutations in liver-metastatic CRC. Therefore, this study aimed to identify and understand the relationship between MSI status and the presence of KRAS mutations in liver-metastatic CRC at our institution.

Materials and Methods

This cross-sectional study was conducted at Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital, Makassar, Indonesia. Patient data were collected from 2021 to 2023. The study sample included all patients with liver-metastatic colon cancer. The estimated number of participants was calculated using Lemeshow's formula [12-14]; the minimum sample size for each group (case and control) was 25 subjects. A consecutive sampling technique was applied in this study.

Liver-metastatic colon cancer

Metastases that were detected at the initial diagnosis of colon cancer (de novo) were categorized as liver-metastatic colon cancer. Colon cancer patients who presented for the first time with radiological signs and clinical symptoms of liver metastasis underwent assessment through abdominal computerized tomography scan, abdominal ultrasound, and abdominal magnetic resonance imaging.

KRAS mutations

KRAS mutations were detected by extracting DNA from paraffin blocks and performing a polymerase chain reaction (PCR). Results are provided on a binary scale (wild-type or mutant).

MSI status

MSI was also detected by extracting DNA from paraffin blocks and performing PCR, with results reported on a binary scale (MSI-low [MSI-L] or MSI-H).

Research procedure

Patients with right or left colon cancer who seek treatment at the Digestive Surgery Department have paraffin blocks collected from biopsy/surgical specimens at the time of initial diagnosis. Subsequently, examination of MSI status and KRAS expression is performed.

Patient Selection

The study included patients with a confirmed anatomic pathological diagnosis of liver-metastatic colon cancer who underwent colon resection. The inclusion criteria were: patients with liver-metastatic colon cancer and resectable liver metastases (defined as having a limited number of metastases, typically up to 3–4 lesions, metastases located in areas of the liver that can be safely resected, and smaller lesions [<5 cm]), absence of extrahepatic metastases, a positive response to neoadjuvant therapy, and a Karnofsky performance status score above 70. Complete clinical data were required for inclusion, and patients with damaged or insufficient paraffin blocks, or those with malignancies in other organs, were excluded.

Specimen Preparation

Paraffin-embedded sections from right or left colon cancer tumors, as well as from liver metastases, were stained with hematoxylin and eosin to assess whether the blocks were suitable for analysis. The paraffin blocks were then sectioned into 10 μm thick slices, which were deparaffinized by soaking in xylene for 30 minutes, followed by treatment with alcohol.

Microdissection and Incubation

After deparaffinization, the tumor tissue was microdissected from the slides. The microdissected tissue was incubated overnight with proteinase K at 55°C to prepare it for further analysis.

DNA extraction procedure and PCR

DNA was extracted from the prepared tissue using the QIAamp DNA FFPE Tissue Kit (QIAGEN). The quality of the extracted DNA was assessed using absorbance ratios (A260/A280 and A260/A230) to ensure it met the criteria for genetic sequencing.

Genetic Analysis

Once the DNA quality was confirmed, genetic sequencing was performed using the AmpliSeq Cancer Hotspot panel v2 for Illumina. This included evaluating KRAS mutations at codons 12 and 13 through PCR and

agarose gel electrophoresis.

Data analysis

Data in this study were collected in tabular form using SPSS version 25.0 (Armonk, NY; IBM Corp.). Univariate and bivariate analyses were conducted. To assess the relationship between MSI status and KRAS mutation status, Fisher's exact test was used. A p-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

Patients with liver-metastatic colon cancer were 16-80 years old and primarily male. Tumors were predominantly located on the left side, of adenocarcinomatous histopathology, and of high histopathological grade (Table 1).

This study also demonstrated that mutant KRAS is most prevalent in the left colon (sigmoid colon cancer), whereas wild-type KRAS is most prevalent in the left colon (ascending colon cancer). We also found that MSI-L tumors are equally prevalent in sigmoid and ascending colon cancer (30% and 33.3%, respectively), while MSI-H tumors are more prevalent in the left colon (sigmoid colon cancer) at 66.7%.

MSI status of liver-metastatic colon cancer

In this study, 18 subjects (31.6%) with liver-metastatic colon cancer had MSI-H tumors (Table 2; Figure 1).

KRAS expression in liver-metastatic colon cancer

In this study, 45 out of 57 subjects (78.9%) with liver-metastatic colon cancer expressed mutant KRAS (Table 3; Figure 2).

Relationship between MSI status and KRAS mutations in liver-metastatic colon cancer

In this study, the majority of patients with MSI-H tumors had mutant KRAS (82%) expression. On the other hand, most MSI-L tumors expressed wild-type KRAS (60%). Fisher's exact test indicated no significant relationship between MSI status and KRAS mutation status in liver-metastatic colon cancer (p = 0.489; Table 4).

Discussion

In this study, liver-metastatic colon cancer was more common in men (54.39%) than women (45.61%), and liver-metastatic colon cancer was more common expressed MSI-L and mutant KRAS. These findings are consistent with the Wu et al. study, which found that although the incidence of colon cancer was higher in men (60.2%), women experienced higher rates of extrahepatic metastasis (28.2% vs. 19.8%) [15, 16]. Additionally, Ardito et al. found that liver-metastatic colon cancer more frequently expressed mutant vs. wild-type KRAS (54.20% vs. 45.80%) and was more common in men than women (62.6% vs. 37.4%) [17].

Table 1. Participant Characteristics

Variable		MSI status			KRAS mutation status		
		MSI-low	MSI-high	p-value	Wild-type	Mutant	p-value
		(n, %)	(n, %)		(n, %)	(n, %)	
Age (years)		55.8 ± 11.8	51.4 ± 15.7		53.3 ± 14.8	47.9 ± 15.0	
	16–25	1 (14)	0 (0)	0.386	1 (2.3)	0 (0)	0.406
	26–35	6 (18)	1 (14.3)		4 (9.3)	3 (42.86)	
	36–45	8 (12)	2 (20)		10 (23.26)	0 (0)	
	46–55	7 (58.3)	5 (41.7)		8 (18.6)	1 (14.28)	
	56–65	10 (76.9)	3 (23.1)		9 (20.93)	3 (42.86)	
	>65	7 (50)	7 (50)		11 (25.8)	0 (0)	
Sex							
	Male	8 (25.8)	23 (74.2)	0.394	23 (74.2)	8 (25.8)	0.516
	Female	10 (38.5)	16 (61.5)		22 (84.6)	4 (15.4)	
Location							
	Right	9 (33.3)	18 (66.7)	0.787	25 (92.6)	2 (7.4)	0.23
	Left	9 (30.0)	21 (70.0)		20 (66.7)	10 (33.3)	
Histopathological type							
	Adenocarcinoma	11 (31.4)	24 (68.6)	0.995	29 (82.9)	6 (17.1)	0.602
	Mucinous	5 (31.2)	11 (68.8)		12 (75.0)	4 (25.0)	
	Signet ring cell carcinoma	2 (33.3)	4 (66.7)		4 (66.7)	2 (33.3)	
Histopathological grade							
	High	8 (44.4)	10 (55.6)	0.178	15 (83.3)	3 (16.7)	0.539
	Moderate	1 (11.1)	8 (88.9)		7 (77.8)	2 (22.2)	
	Low	1 (20)	4 (80.0)		5 (100)	0 (0)	

Note: MSI, microsatellite instability; KRAS, Kirsten rat sarcoma viral oncogene.

Table 2. Frequency Distribution of MSI Status in Liver-metastatic Colon Cancer

MSI status	n	%
MSI-low	39	68.4
MSI-high	18	31.6

Note: MSI, microsatellite instability.

Table 3. Frequency Distribution of KRAS Mutations in Liver-metastatic Colon Cancer

KRAS expression status	n	%
Wild-type	12	21.1
Mutant	45	78.9

Note: KRAS, Kirsten rat sarcoma viral oncogene.

With respect to age, our study demonstrated that the incidence of colon cancer increases with age after age 25. Specifically, there is only one case in the 18-25-year-old age group, but at least seven cases in the 25-and-above age group. Mangi et al. also showed that the prevalence of CRC is higher in individuals aged 25 and above (81.6%) [18]. With respect to cases of liver-metastatic colon cancer, this finding aligns with studies by Ituarte et al. and Xu and Wang, which found the highest incidence in individuals over 44 years old [15, 16]. According to Gao et al., the incidence of liver-metastatic colon cancer in younger patients may be due to high rates of misdiagnosis and relatively rapid disease progression. Additionally, colon cancer in younger individuals is generally moderately to poorly differentiated, making it more likely to metastasize [19].

The data in this study show that mutant KRAS is more prevalent in left-sided colon cancer. This finding is consistent with those of Diener and Fichtner-Feigl, in which the prevalence of mutant KRAS was 30–45% in CRC and 25–52% in liver-metastatic CRC [20]. Additionally, in an analysis of 552 Polish CRC patients, Ciepiela et al. found that there were more cases of left-sided colon cancer (45.2%, p = 0.0002) among liver-metastatic (54.5%) and KRAS-mutant (42.8%) cases. In their analysis, colon cancer was not homogeneous; rather, cancer development was closely related to its location [21]. This finding differs from that of Xie et al., in which mutant KRAS was more common in right-sided colon cancer (p = 0.010) [22]. Specifically, in the study by Xie et al., there were 32 subjects with mutant KRAS out of a total of 37 right-sided colon cancer patients, and 30 subjects with mutant KRAS out of 79 left-sided colon cancer patients [22].

Another finding in this study indicates that MSI-H tumors are equally prevalent in patients with right- and left-sided colon cancer (9 subjects in each group), but MSI-L tumors are more prevalent in patients with left- vs. right-sided colon cancer (70% versus 66.7%). This finding

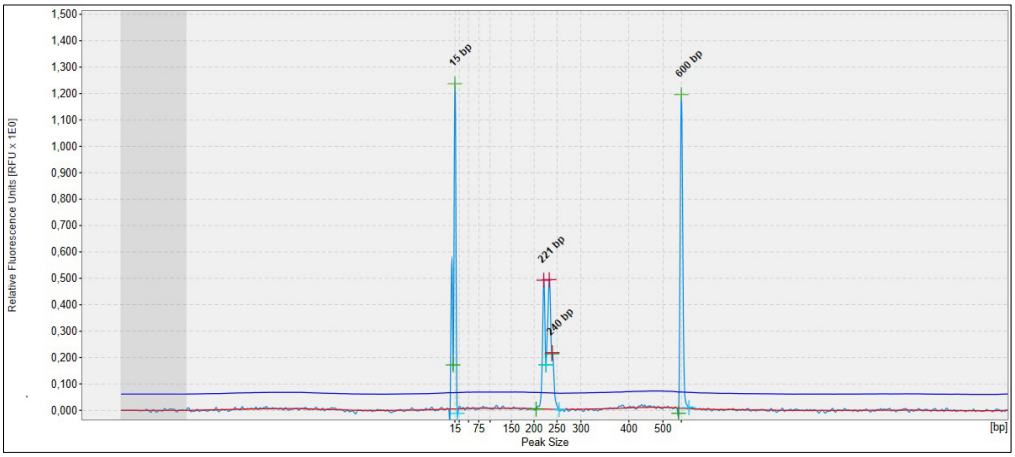

Figure 1. Electropherogram Depicting MSI in Liver-metastatic Colon Cancer

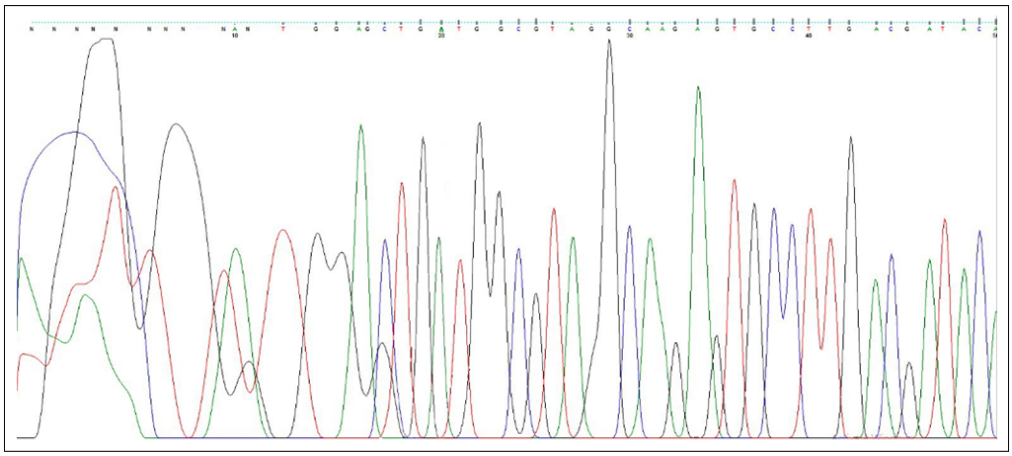

Figure 2. Electropherogram of KRAS Expression in Liver-metastatic Colon Cancer

Table 4. Relationship between MSI and KRAS Mutation Status in Liver-metastatic Colon

MSI status	Mutant KRAS n (%)	Wild-type KRAS n (%)	p-value
MSI-high	32 (82)	7 (18)	0.489
MSI-low	13 (60)	5 (40)	

Note: MSI, microsatellite instability; KRAS, Kirsten rat sarcoma viral oncogene.

is consistent with that of Han et al., in which MSI-L tumors were more prevalent in left-sided colon cancer cases [23]. MSI-H tumor distribution differs between right- and left-sided colon cancer. Right-sided MSI-H tumors are more prevalent and often exhibit aggressive features, including higher tumor stages and increased mucinous carcinoma types [24]. Right-sided colon cancers show a higher prevalence of the CpG island methylator phenotype (CIMP) and are often hypermutated, leading to a more aggressive tumor behavior [25]. MSI-H tumors are characterized by a deficiency in MMR mechanisms, leading to an accumulation of mutations in microsatellite regions [26, 27]. Furthermore, right-sided tumors are associated with hypermethylation and a hypermutated state, contributing to poorer prognoses [25]. MSI-H tumors often present with distinct clinical features, such as poorly differentiated histology and a bimodal age distribution [26, 28]. In contrast, left-sided colon cancer has a lower prevalence of MSI-H tumors, with only 10-15% of cases showing high levels of microsatellite instability. Left-sided MSI-H tumors tend to have lower tumor stages and less frequent abnormal carcinoembryonic antigen levels [24]. Left-sided colon cancers have less frequent methylation of human mutL homolog-1 and lower CIMP rates, indicating a different pathway for MSI acquisition [29]. This difference in distribution may impact treatment strategies and prognosis for patients with colon cancer, as MSI-H tumors have been shown to respond differently to certain types of chemotherapy and immunotherapy [30, 31]. Understanding the distribution of MSI-H tumors in right- and left-sided colon cancer is important for guiding personalized treatment approaches for patients with this disease. The distribution of MSI-H tumors varies significantly between right- and left-sided colon cancers, reflecting distinct biological and clinical characteristics.

The relationship between MSI and KRAS mutations appears complex, with some studies indicating no statistically significant association. For instance, in a study of CRC patients from Tunisia, no significant associations were found between KRAS mutations and MSI status despite KRAS mutations in 31.5% of cases [29]. Additionally, a large analysis of CRCs showed that while KRAS mutations were common, their prognostic significance varied between MSI and MSS groups, with no significant differences in survival outcomes for MSI patients [32]. Conversely, another study indicated that while KRAS mutations were prevalent in MSI gastric cancer, they were associated with poorer outcomes in microsatellite stable (MSS) cases [33]. Additionally, a large analysis of CRCs showed that while KRAS mutations were common, their prognostic significance varied between MSI and MSS groups, with no significant differences in survival outcomes for MSI patients [34]. This suggests that while KRAS mutations can coexist with MSI, their clinical implications may differ significantly based on the tumor's MSI status. This study also found that KRAS mutations (17.1%) were more prevalent in adenocarcinomatous tumors (61.4%). This result is consistent with that of Ciepiela et al., in which most tumors (98.9%) were adenocarcinomas, followed by medullary carcinomas (0.2%), neuroendocrine tumors, and goblet cell carcinoid tumors [21]. Alexander et al. also reported a higher proportion of high-grade, MSI-H adenocarcinomatous tumors (38%) [35]. Thus, the findings of this study are consistent with those in the literature in that adenocarcinoma was the most prevalent histopathological type (35%).

MSI and KRAS mutations are critical biomarkers in liver-metastatic CRC, influencing treatment outcomes and survival rates. Studies indicate that MSI-positive tumors exhibit a higher prevalence of KRAS mutations, with 66.7% in MSI-positive versus 52.3% in MSS cases [36]. In a large cohort from the National Cancer Database, the prevalence of MSI-H was 3.1%, while KRAS mutations were found in 42.4% of patients. Notably, geographic discrepancies exist, with higher MSI rates in certain United States regions. Furthermore, KRAS mutations are associated with poorer overall survival, particularly in right-sided CRC [37]. The interaction between these biomarkers is crucial, as they can affect treatment responses, such as resistance to therapies in Raf murine sarcoma viral oncogene homolog B (BRAF)-mutant cases with concurrent KRAS mutations [38]. The lack of association between MSI status and KRAS mutations in liver-metastatic CRC can be attributed to several biological factors. Firstly, studies indicate that KRAS mutations do not significantly influence survival outcomes in patients with synchronous liver metastases, regardless of tumor sidedness [39]. Additionally, while KRAS mutations are linked to poorer recurrence-free survival in left-sided tumors, this association is not observed in right-sided tumors [40]. Furthermore, the interplay between KRAS status and tumor laterality suggests that the biological behavior of tumors may differ based on their location, complicating the relationship with MSI [41]. Lastly, other mutations, such as BRAF, may also interact with KRAS status, further obscuring the association with MSI [42]. These findings highlight the complexity of genetic interactions in CRC, suggesting that the absence of a clear link between MSI and KRAS mutations may reflect underlying biological diversity rather than a straightforward relationship. Conversely, some studies have shown that MSI status can influence

treatment responses and outcomes, indicating that while KRAS mutations may not correlate with MSI, they still play a critical role in the overall prognosis of CRC patients with liver metastases [43].

CRC metastasis to the liver exhibits significant genomic diversity, particularly in Asian populations. In a study of Chinese patients, KRAS mutations were found in 42% of colorectal liver metastases, with tumor protein p53 and adenomatous polyposis coli mutations also prevalent [44]. KRAS mutations correlate with poorer overall survival and disease-free survival, especially in KRAS-mutated tumors, where surgical margins do not significantly impact outcomes [45]. Notably, the KRAS A146 mutation is associated with higher tumor burden and inferior survival compared to other variants [46]. Furthermore, the presence of KRAS mutations influences surgical strategies, although the type of resection may not significantly affect survival outcomes in KRAS-mutated cases [47]. These findings underscore the importance of understanding KRAS mutation status in managing CRC metastasis to the liver in Asian populations, particularly regarding personalized treatment approaches and surgical decisions.

This study has several limitations. First, the sample size is low, 57 patients. Second, it is subject to selection bias, given its retrospective nature. Specifically, most cases were diagnosed at advanced stages. Third, some patients may have been lost to follow-up, potentially leading to lost medical records and data. Fourth, statistical methods highlight the need for more robust analyses in future research. Therefore, more research is needed, particularly in prospective studies with larger sample sizes, to clarify the role of gene mutations in CRC prognosis and implications for personalized medicine or targeted therapies.

In conclusion, we conclude that there is no significant relationship between MSI status and KRAS mutation status in liver-metastatic CRC ($p = 0.489$). We found that 31.6% of tumors were MSI-H and that 78.9% expressed mutant KRAS, with a majority of MSI-H tumors also having mutant KRAS.

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Conflicts of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Ethics approval

This study was approved by the Medical Research Ethics Commission of the Medical Faculty of Hasanuddin University (number: 850/UN4.6.4.5.31/PP36/2023). We promised that the participants' data were anonymized or maintained with confidentiality, the rights or interests of participants were not invaded, and informed consent was taken from all individual participants.

Authors' contributions

APP: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

WS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Software, Validation, Visualization, Writing – original draft.

JAU: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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MF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing.

All authors read and approved the final version of the manuscript.

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