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Clinicopathological analysis of giant ovarian tumors

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ABSTRACT

Objective: This study aims to analyze giant ovarian tumors' clinical and pathological characteristics.
Material and Methods: This was an analytical observational study. Medical records of all patients with giant ovarian tumors who underwent surgery between January 2020 and June 2022 at Dr. Soetomo Academic Hospital, Surabaya, Indonesia, were analyzed.
Results: We analyzed 63 patients with ovarian tumors measuring > 20 cm who underwent surgery at Dr. Soetomo Academic Hospital, Surabaya, Indonesia. The mean tumor size was 25.9 cm (largest size was 41 cm). There was no significant difference in tumor size between benign and malignant giant ovarian tumors ($p = 0.261$). Based on histopathological results, 66.67 % of giant ovarian tumors were malignant, 26.98 % were benign, and 6.35 % were borderline. Among the malignant tumors, the epithelial type accounted for 69 % of cases. Most giant ovarian tumors originated in the left adnexa (68.25 %). There was no significant difference in patient age ($p = 0.511$), tumor size ($p = 0.168$), malignancy ($p = 0.303$), and histopathological type ($p = 0.232$) regardless of adnexal side. CA125 levels did not differ significantly between malignant and benign giant ovarian tumors ($p = 0.604$). There was no correlation between malignant ovarian tumor size and CA125 levels, while there was a significant difference between CA125 levels and the adnexal side ($p = 0.010$).
Conclusions: Most giant ovarian tumors were malignant, diagnosed at an early stage, and predominantly epithelial type. CA125 levels did not correlate with the size of malignant ovarian tumors. Most giant ovarian tumors originate in the left adnexa.

Introduction

In 2020, 313,959 new cases of ovarian cancer were diagnosed worldwide, with an age-standardized incidence of 6.6 per 100,000 [1]. Of all ovarian malignancies, 88.4 % are epithelial cancers, and the most prevalent histological categories are mucinous (15 %) and serous (65.9 %) carcinomas [2].

Adnexal masses can be benign, borderline, or malignant, originating from the ovary and fallopian tubes [3]. Among the benign ovarian tumors, serous ovarian cystadenoma is the most common, followed by mucinous ovarian cystadenoma and dermoid [4]. Malignant ovarian tumors can be divided into epithelial ovarian cancer, germ cell tumors, sex cord-stromal tumors, and metastatic tumors [3]. Bloating, an enlarged abdomen, weariness, urinary tract problems, and pelvic or abdominal discomfort are the most common ovarian cancer symptoms [5]. Localized ovarian malignancies have few or no symptoms, which may delay the application of appropriate diagnostic imaging techniques [6].

The diagnosis of ovarian tumors can be confirmed by physical examination, ultrasonography, computed tomography, or magnetic resonance imaging. Suspicion of ovarian tumor malignancy can be assessed from radiological imaging of the tumor and elevated tumor markers such as cancer antigen 125 (CA125), carcinoembryonic antigen (CEA), beta human chorionic gonadotropin (Beta-hCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH) [3,7].

Surgery is the cornerstone of ovarian tumor management. Surgical staging is crucial for accurately determining the disease stage, the extent of surgery, and the need for adjuvant treatment [7]. An important objective of surgery for early-stage ovarian tumors is to determine the disease stage definitively. In contrast, an important aim of surgery for advanced-stage ovarian tumors is complete resection [8].

Tumor size is an important factor to consider when deciding on

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clinical treatment. Tumors with a diameter > 10 cm that cause complaints can be indicated for surgical treatment. Tumor size as a predictor of malignancy in ovarian tumors remains debatable. One study showed that including tumor size in the risk of malignancy index calculation did not increase performance, but another study showed otherwise [9,10]. Large ovarian tumors can be benign or malignant [11]. One study showed that early-stage ovarian cancer had a larger tumor size than advanced-stage ovarian cancer [12]. To date, there is no standard definition or parameter for large ovarian tumors. The ovarian tumor is considered large if the size is > 10 cm or above the umbilicus [13]. Another publication considered an ovarian mass between 5 and 15 cm as large, and if the diameter was > 20 cm, it was considered giant [14]. Histopathological analysis of large ovarian tumors showed that the most common type was a mature teratoma, followed by mucinous and serous cystadenomas. In contrast, another study showed that the most common type of larger ovarian tumor was a benign teratoma, followed by serous cystadenoma and endometriotic cysts [13,15]. Other case reports of large ovarian tumors have shown other histopathological types, including fibromas, seromucinous adenocarcinomas, and low-grade mucinous papillary cystadenocarcinomas [11].

Clinical and pathological mapping of giant ovarian tumors is important for analyzing the incidence and prevalence among all patients with ovarian tumors, the clinical characteristics and size, side of adnexal involvement, and histopathological type. Understanding clinical trends and histopathology can provide an overview of the management and prognosis of patients with giant ovarian tumors.

Material and methods

This study was an observational study of all patients with giant ovarian tumors at Dr. Soetomo Hospital Surabaya in Indonesia between January 2020 and June 2022. We observed several clinical parameters, including patient age, tumor size, involved adnexal side, CA125 level, tumor stage, and histopathological type.

Data were collected from the medical records of patients diagnosed with giant ovarian tumors who underwent surgery in 2020–2022 at Dr. Soetomo Hospital in Surabaya, Indonesia. Only tumors with a diameter > 20 cm were considered giant and included in this study.

All statistical analyses were performed using the Statistical Package for Social Scientists (SPSS) version 25 to assess the frequency distribution and bivariate analysis with an independent t-test. In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for additional data analysis or the reproducibility of this study in other centers if requested.

This study was approved by the ethics committee of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia (registration number: 1635/104/4/IX/2022). The ethics committee of Dr. Soetomo General Academic Hospital waived the need for informed consent because of the study's retrospective nature. Patient confidentiality was guaranteed.

Results

Sixty-three patients with ovarian tumors > 20 cm in size were included in this study. The patients underwent surgery at Dr. Soetomo Academic Hospital, Surabaya, Indonesia. The average patient age was 38 years (11–66 years). The histopathological tumor type in the youngest patient was embryonal cell carcinoma, and that in the oldest patient was granulosa cell tumor.

The average tumor size was 25.9 cm (20–41 cm). The average tumor sizes were 26.61 and 24.91 cm for malignant and benign tumors, respectively. There was no significant difference in tumor size between benign and malignant giant ovarian tumors (p = 0.261; Table 1).

Based on histopathological results, among the 63 giant ovarian tumors, 42 were malignant (66.67 %), 17 were benign (26.98 %), and four were borderline (6.35 %). Among the 13 patients with non-epithelial malignant ovarian tumors, the most dominant type was granulosa cell tumors in five patients (38.5 %), followed by yolk sac tumors in four patients (30.8 %), and an immature teratoma, dysgerminoma, embryonal cell tumor, and mixed tumor in only one patient for each type (7.7 %) (Table 2).

Table 1
Bivariate analysis between malignancy and tumor size.

	Malignant (Mean + SD)	Benign (Mean + SD)	P value
Tumor size	26.61 + 5.74	24.91 + 6.1	0.261*
Patient's age	38.17 + 14.39	37.29 + 12.03	0.841*

* Independent t-test

We used FIGO (*The International Federation of Gynecology and Obstetrics*) staging type for classification. Among the 42 patients with malignant giant ovarian tumors, 28 were in stage I (66.7 %), 10 in stage II (23.8 %), 3 in stage IV (7.14 %), and 1 in stage II (2.38 %). Based on histopathological types, among the 42 patients with malignant ovarian tumors, 29 (69.05 %) had epithelial malignant ovarian tumors, and 13 of them were non-epithelial type (30.95 %). Seventeen patients had malignant ovarian tumors that were mucinous type (40.48 %) (Table 3).

Of the 63 giant ovarian tumors, 43 originated from the left (68.2 %) and 20 originated from the right (31.8 %) adnexa. There were no significant differences in patient age (p = 0.511), tumor size (p = 0.168), malignancy (p = 0.303), or histopathological type (p = 0.232) between either adnexal side (Table 4).

Only patients under 30 years old were assessed for all tumor markers, including CA125, CEA, LDH, beta-hCG, and AFP, among all the study samples. Due to cost constraints, patients over 30 years old are only tested for the tumor marker CA125, not for any additional tumor markers (Table 5; Table 6).

Non-epithelial type ovarian tumors had increased levels of beta-hCG, AFP, and LDH. Epithelial and non-epithelial ovarian cancers significantly differ in AFP levels (Table 7).

Due to the lack of comprehensive tumor marker data, we decided to concentrate on a study of CA125 values. The average CA125 level was 864.98 units/mL (13.86–33140 units/mL). CA125 levels did not differ significantly between malignant and benign giant ovarian tumors (p = 0.604). There was no correlation between tumor size and CA125 levels in giant ovarian tumors (p = 0.308). A significant difference was observed between CA125 levels and the involved adnexal side (p = 0.010). Right adnexal involvement showed higher CA125 levels in the tumor (mean: 1871.95 unit/mL) compared to those with left adnexal involvement (mean: 396.62 unit/mL) (Table 8).

Table 2
Descriptive data of giant ovarian tumors.

Variable		N (%) of all	
Patient's age	10-20 y.o	7 (11.11 %)	
	21-30 y.o	13 (20.63 %)	
	31-40 y.o	16 (25.40 %)	
	41-50 y.o	13 (20.63 %)	
	51-60 y.o	10 (15.87 %)	
	> 60 y.o	4 (6.36 %)	
Malignancy	Benign	17 (26.98 %)	Endometriosis (7)
	Borderline	4 (6.35 %)	Mucinous (4)
	Malignant	42 (66.67 %)	Serous (3)
			Mature teratoma (3)
			Serous (2)
			Mucinous (2)
			Epithelial (29)
			Non-Epithelial (13)
Tumor type	Epithelial	47 (74.60 %)	
	Non-epithelial	16 (25.40 %)	
Involved adnexa	Left adnexa	43 (68.25 %)	
	Right adnexa	20 (31.75 %)	

Table 3
Descriptive data of malignant giant ovarian tumors.

Variable		N (%) of all	% of each histopathological type
Stage	Stage I	28 (66.67 %)	
	Stage II	1 (2.38 %)	
	Stage III	10 (23.81 %)	
	Stage IV	3 (7.14 %)	
Histopathological type			
Epithelial (29)	Serous	5 (11.90 %)	(17.24 %)
	Mucinous	17 (40.48 %)	(58.62 %)
	Endometrioid	2 (4.77 %)	(6.9 %)
	Clear cell	5 (11.90 %)	(17.24 %)
Non-Epithelial (13)	Immature Teratoma	1 (2.38 %)	(7.7 %)
	Granulosa cell tumor	5 (11.90 %)	(38.5 %)
	Dysgerminoma	1 (2.38 %)	(7.7 %)
	Yolk Sac	4 (9.53 %)	(30.8 %)
	Embryonal cell	1 (2.38 %)	(7.7 %)
	Mixed tumor	1 (2.38 %)	(7.7 %)

Table 4
Analysis between involved adnexal side, patient's age, and tumor characteristics.

	Type	Right	Left	P-value
Patient's age		40.55 + 14.07	37.60 + 14.04	0.511*
Tumor size		25 (20-40)	25 (20-41)	0.168 **
Malignancy	• Benign • Malignant • Borderline	3 (4.8 %) 16 (25.4 %) 1 (1.6 %)	14 (22.2 %) 26 (41.3 %) 3 (4.8 %)	0.303#
Histopathological type	• Epithelial • Non-Epithelial	13 (20.6 %) 7 (11.1 %)	34 (54 %) 9 (14.3 %)	0.232 ##

* Independent t-test
** Man-whitney
\# Kruskal-wallis test
\## Chi-square test

Discussion

Based on our findings, the majority of giant ovarian tumors are malignant and diagnosed at an early stage (stage I). Most lesions were epithelial and mucinous, with left adnexal involvement. There were no statistically significant differences between malignant and benign giant ovarian tumors in terms of tumor size, patient age, or CA125 levels. CA125 levels were also unrelated to tumor size. There were no significant differences in patient age, tumor size, histopathological type, or malignancy between left and right adnexal involvement; however, right adnexal involvement was associated with higher CA125 levels.

There are no publications on the analysis of giant ovarian tumors at a specific age. Several case reports of giant ovarian tumors have been published, and the ages of patients in these reports varied from children to older women [11,16]. Based on this study, giant ovarian tumors may occur at any age from 11–66 years. The youngest patient's histopathological type was embryonal cell carcinoma, and the oldest was a granulosa cell tumor. The histopathological types in several reports of giant ovarian tumors in women > 60 years old were ovarian cystadenocarcinoma, benign serous cystadenoma, and metastatic adenocarcinoma from rectal cancer [16,17]. The mean age of patients with giant ovarian tumors in this study was 38 years. There have been no publications on the average age of patients with giant ovarian tumors.

The size of an ovarian tumor does not determine its malignancy. Several tools for estimating the malignancy of ovarian cancer, such as the risk malignancy index and risk of ovarian malignancy algorithm, do not include tumor size as a parameter for predicting whether ovarian tumors are malignant [19]. The International Ovarian Tumor Analysis group's 10 Simple Rules for evaluation of adnexal lesions include tumor size as one of the parameters determining malignancy; however, in this calculation, size is not purely a determinant, but other parameters include size, namely the presence or absence of solid parts and unilocular or multilocular tumors [20]. Most giant ovarian tumors exhibit benign characteristics, with only a minority demonstrating malignant properties. To the best of our knowledge, only a limited number of studies have reported the presence of large malignant ovarian tumors [11]. Our findings showed that giant ovarian tumors can be benign or malignant, and most giant ovarian tumors in this study were malignant (67 %).

In cases of ovarian cancer in younger patients, the symptoms that a patient encounters are impacted by the size of the tumor as well as its pathology. On the other hand, symptoms alone are not sufficient to determine the malignancy of the ovarian tumor. There is a high probability that a malignant ovarian tumor would be significantly larger than 10 centimeters, will be bilateral, and not well circumscribed [18].

Our study showed that most malignant giant ovarian tumors were stage I (66.7 %). Women with early-stage ovarian cancer have larger ovarian tumors than those with advanced-stage ovarian cancer [12]. One possible theory regarding this is that advanced-stage tumors spread when the tumor is still relatively small. In contrast, early-stage tumors develop locally and continue to grow in size without spreading to other tissues. Advanced ovarian cancer may produce substances that cause metastasis, whereas early-stage ovarian cancer may not secrete these substances.

In this study, malignant ovarian tumors were primarily epithelial type (69 %), and only 31 % were non-epithelial. Epithelial ovarian cancer is more common than the non-epithelial type, and 95 % of ovarian malignancies are epithelial type [21]. To the best of our knowledge, no published studies have compared the proportion of epithelial and non-epithelial types among giant ovarian tumors. According to our study, both epithelial and non-epithelial ovarian cancers can develop into giant ovarian tumors.

Our study showed that mucinous ovarian tumors were the most common type of giant malignant ovarian tumors (40.48 %), which is in accordance with the literature showing that mucinous ovarian tumors are usually large, with an average size of 18 cm [22]. The size of mucinous ovarian tumors can be used as an early indicator of whether the mucinous ovarian cancer is primary or metastatic. Most primary ovarian cancers are unilateral tumors of > 10 cm [22]. Our study confirms that mucinous ovarian tumors tend to be large, even if malignant.

Molecular research has provided insights into several features of ovarian cancer, resulting in the categorization of epithelial-type ovarian cancer into two distinct types: type I ovarian cancer and type II ovarian cancer [23]. The subtypes of ovarian cancer classified as type I are low-grade serous, mucinous, endometrioid, and clear cell carcinoma. From a clinical perspective, Type I tumors are believed to manifest as large tumors, one-sided cystics that are limited to the ovary. These tumors are often considered low-grade, exhibiting less aggressive clinical

Table 5
Characteristic of tumor markers level giant ovarian tumor under 30 years old.

No.	Histopathology	CA125	CEA	LDH	Beta-hCG	AFP
1.	clear cell carcinoma	78,50	1,97	248,00	0,59	1,30
2.	endometrioma	33140,00	2,59	165,00	0,30	1,60
3.	mixed germ cell	431,50	< 0,5	1906,00	0,50	27,60
4.	mucinous carcinoma	71,70	0,05	168,00	0,20	1,40
5.	mucinous carcinoma	50,70	3,72	551,00	0,20	1,30
6.	endometrioma	291,00	1,07	225,00	0,30	0,90
7.	endometrioma	366,40	1,64	207,00	0,40	0,40
8.	mucinous carcinoma	116,50	5,24	208,00	0,30	1,66
9.	dysgerminoma	230,00	< 0,5	6185,00	190,40	1,30
10.	mucinous borderline	104,60	2,00	160,00	0,30	1,40
11.	yolk sac tumor	125,00	0,50	405,00	3307,00	78019.2
12.	immature teratoma	170,50	12,52	185,00	0,30	21,80
13.	mucinous carcinoma	136,80	10,10	194,00	0,20	1,40
14.	yolk sac tumor	341,10	1,18	541,00	0,20	3467,90
15.	yolk sac tumor	282,65	1,00	187,00	0,30	23813,50
16.	mature teratoma	14,60	8,24	162,00	0,20	20,60

Table 6
Statistic distribution of tumor markers level giant ovarian tumor under 30 years old.

	Mean	Median	Minimum	Maximum	SD
CA125	2246,97	153,65	14,6	33140	8239,07
CEA	3,30	1,80	0,05	12,52	3,79
LDH	731,06	207,50	160	6185	1516,76
Beta- hCG	218,86	0,3	0,2	3307	824,87
AFP	6586,45	1,5	0,4	78019,20	19953,29

Table 7
Bivariate analysis between histopathology and tumor markers.

	Epithelial Median (min-max)	Non Epithelial Median (min-max)	P value
CA125	116,5 (50,7-33140)	230 (14,6-431,5)	0536
CEA	2,0 (0,05-10,10)	1,0 (0,5-12,52)	0408
Beta-hCG	0,3 (0,2-0,59)	0,3 (0,2-3307)	0470
AFP	1,4 (0,4-1,66)	27,6 (1,3-78019,2)	0005
LDH	207 (160-551)	405 (162-6185)	0351

*Man-Whitney test

Table 8
Analysis between Ca125 level and tumor characteristics.

	Malignant Median (Min-Max)	Benign Median (Min-Max)	P-value
CA125 level	138.5 (23.57-6554.3)	71.9 (13.86–33140)	0.604*
	Right	**Left**	
CA125 level	147.35 (13.86-33140)	128.94 (14.6-6554.30)	0.010*
	Tumor size of malignant tumor Median (Min-Max)		
CA125 level	138.5 (23.57-6554.3)		0.308**

* Man-Whitney test
** Pearson correlation test

behavior and a more favorable prognosis. There is a hypothesis suggesting that Type I neoplasms originate from non-cancerous lesions outside the ovaries, which then become embedded in the ovaries and eventually evolve into malignant tumors [24]. Type II epithelial ovarian cancer encompasses high-grade serous carcinomas, undifferentiated carcinomas, and carcinosarcomas [23]. Type II tumors have a higher level of aggressiveness, are typically detected at more advanced stages, and display a significant degree of genetic instability. Most of these tumors include mutations in the TP53 gene, and nearly half of the cases show mutations, hypermethylation, or malfunction in the breast cancer gene BRCA1/2 [23]. There is a widely held belief that certain Type II epithelial ovarian cancers (EOC) originate from aberrant cells in the fallopian tube lining known as serous tubal intra-epithelial lesions (STIL), which then evolve into serous tubal intra-epithelial carcinomas (STIC) [24]. In this study, type I were found in 60,31 % of giant ovarian cancers, and type II were counted in 14,28 % cases.

Among giant non-epithelial ovarian tumors, granulosa cell tumors were the most common type (38.5 %). One study showed that the mean size of ovarian granulosa cell tumors was 11.8 cm (range: 5–27 cm) [25]. The second most common giant malignant ovarian tumor in our study was an endodermal sinus tumor. Another type of giant ovarian tumor is ovarian dysgerminoma, which can grow very rapidly and is very large, up to 50 cm in size, as shown in our study [26].

Borderline ovarian tumors can also be very large, and a case report showed a mucinous borderline ovarian tumor measuring 60 × 50 × 40 cm [27]. In our study, there were four borderline ovarian tumors (6 %), which is consistent with a systematic review by Grigore et al. that showed the proportion of borderline ovarian tumors was approximately 3.4 % of all ovarian tumors > 10 cm [13].

The laterality (right or left) of giant ovarian tumors has not been well studied. Several case reports have shown that giant ovarian tumors originate on the left side [11,28], while other publications have reported that giant ovarian tumors originate from the right side [16,27]. Our study showed that most giant ovarian tumors (68.2 %) originated in the left ovary. From our findings, the origin of the tumor, whether from the right or left ovary, was not related to the malignancy of giant ovarian tumors. Furthermore, our findings showed that tumor size was unrelated to laterality or histopathological type.

Our study showed that CA125 levels did not correlate with the size of giant malignant ovarian tumors. Prior research has not investigated the correlation between the size of malignant ovarian tumors and CA125 levels, as our study did. Only one study showed that a higher CA125 level was associated with larger borderline ovarian tumors [29]. Studies showed that CA125 levels are more strongly related to the prediction of successful cytoreductive surgery, metastasis, and survival [30]. Our study's comparative analysis of CA125 levels between benign and malignant giant ovarian tumors showed no significant differences. However, CA125 levels in malignant ovarian tumors tended to be higher than those in benign ovarian tumors. Another study on borderline ovarian tumors showed that tumor size positively correlated with CA125 levels [29]. This study analyzed only borderline tumors and did not include other histopathological types. In our study, CA125 levels do not correlate or predict tumor size but can be a predictor of treatment responses and survival.

Due to financial constraints, our study could not analyze tumor markers other than Ca125. Consequently, tests for markers other than Ca125 were only conducted on patients under 30. Examination of tumor markers in individuals below the age of 30 revealed a notable disparity

in AFP levels across epithelial and non-epithelial tumor types.

High-grade serous ovarian cancer is the predominant form of epithelial ovarian cancer, accounting for 70 % of cases. Additionally, 90 % of all ovarian cancer cases are of the epithelial type [31]. Alterations in the fallopian tubes are a contributing factor to the development of high-grade serous ovarian cancer, beginning with the presence of serous tubal intra-epithelial carcinomas (STIC). Salpingectomy has been linked to a significant reduction in the risk of ovarian cancer, estimated to be over 80 % [32]. Research has shown that salpingectomy is a safe and cost-effective procedure that does not lead to an earlier onset of menopause. Additional research is required to determine if salpingectomy can effectively prevent particularly big ovarian cancer.

Our study included all cases of giant ovarian tumors with a minimum diameter of 20 cm, providing a summary of the characteristics and features of giant ovarian tumors. Our study also evaluated the role of CA125 in giant ovarian tumors. The obvious limitation was that our study did not include survival as a parameter. Survival parameters were difficult to analyze because many patients lost follow-up and changed addresses/phone numbers during study periods. However, this did not significantly impact the study because we focused on clinical characteristics, not survival.

In clinical practice, the findings of this study have immediate and tangible implications for the diagnosis and management of giant ovarian tumors. By examining these clinicopathological characteristics, practitioners can make more precise and individualized treatment decisions. This may improve patient outcomes and optimize therapeutic strategies. The findings of this study may also influence surgical techniques and postoperative care protocols.

Given the complexity of ovarian tumors, a multidisciplinary approach represents the most effective way to care for patients. In particular, a medical oncologist must collaborate with a gynecologic oncologist, radiologist, pathologist, and other specialists, as it allows for the development of personalized care plans and prescriptions for each patient. Moreover, multidisciplinary team meetings and continuous patient experience discussions enable accurate diagnosis and treatment options [33].

Conclusion

Clinical and pathological mapping of giant ovarian tumors is important for analyzing the incidence and prevalence among all patients with ovarian tumors, the clinical characteristics and size, side of adnexal involvement, and histopathological type. Understanding clinical trends and histopathology can provide an overview of the management and prognosis of patients with giant ovarian tumors. This study shows that most giant ovarian tumors are malignant and diagnosed at an early stage. They are commonly epithelial types and mostly involve the left adnexa. CA125 levels did not correlate with the size of malignant ovarian tumors.

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CRediT authorship contribution statement

Renata Alya Ulhaq: Writing – review & editing, Project administration. **Hanif Ardiansyah Sulistya:** Writing – review & editing. **Brahmana Askandar Tjokroprawiro:** Writing – original draft, Supervision, Methodology, Conceptualization. **Khoirunnisa Novitasari:** Writing – original draft, Formal analysis, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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