Regional lymph node infiltration and thick lesions are associated with poor prognosis in high-risk resected melanomas: A retrospective cohort study

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ABSTRACT
Background: Acral lentiginous and mucosal melanoma that represent lesions without cumulative sun-induced damages account for 65% of melanomas among Asians but constitute only 5% in Caucasians. The distinct clinical manifestations might influence the clinical course, response to treatment, and outcomes. Factors associated with the prognosis of high-risk resected melanoma in Asians are still rarely reported.

Methods: Clinical, histological determinants of non-distant metastatic melanoma patients who underwent complete resection in 2014–9 were analyzed.

Results: Mucosal melanoma, nodular melanoma, and acral lentiginous melanoma accounted for 45.1%, 40.2%, and 14.2% of total melanoma cases (N = 82), respectively. Among cutaneous melanomas, all patients were diagnosed with Breslow’s depth more than 4 mm (T4), 51% with ulceration, 95.6% with diameter more than 6 mm, 59% with lympho-vascular invasion, and 74% with regional lymph node infiltration. In mucosal melanomas, 78.3% were diagnosed in advanced stages, 14.5% with regional spread to lymph nodes and 77% with regional infiltration beyond mucosa. Lesions with ulceration were associated with higher risk of distant metastasis (OR 3.003, 95%CI:1.01–9.09). Infiltration into regional lymph node was associated with shorter overall survival (median survivals were 17 vs 23.4 months, Mantel-Cox test P = 0.049). Patients diagnosed at Breslow T4 were also associated with poorer overall survival than T1-3 (median survivals were 23 vs 32 months, Mantel-Cox test P = 0.047).

Conclusion: The majority of melanoma patients in our population were diagnosed in advanced stages with a higher risk for recurrence and progression into distant metastasis. Regional lymph node involvement and thicker tumor (T4) were associated with poor prognosis.

1. Introduction

Melanoma is the most potentially lethal form of skin cancer that develops through uncontrolled melanocyte proliferation [1]. Although melanoma is traditionally considered as a rare cancer with around 270,000 new cases per year worldwide, the incidence has risen much higher than any other cancer [1,2]. Risk factors, incidence, and clinical manifestations of melanoma vary greatly by regions, ethnicity, age, and sex [3]. In Caucasians, 90% of melanoma cases originate from the sun-exposed skin and predominantly present as superficially spreading melanomas. In Asians, cutaneous melanomas (CM) are primarily manifested as acral lentiginous melanoma (ALM) [4] and nodular melanoma (NM) [4,5]. In addition, mucosal melanomas (MM) constitute almost a quarter of all melanomas among Asians [4,6]. Both MM and acral melanomas contribute only 5% of cases in Caucasians [7].

Current evidence has shown that ALM, NM, and MM have specific patterns of underlying genetic mutations, clinical course, and relatively worse prognosis [8–10]. Localized melanomas are considered curable using current treatment approaches of wide local excision with sufficient safety margins and adjuvant treatments. However, disease recurrence and progression are relatively high reaching 13.4% in the first two years.
2.2. Data processing

Clinical, pathological, and follow-up data including age, sex, Breslow thickness, stage, histological subtype, regional lymph node involvement were extracted from the medical records. Surveillance after acute treatment was performed according to national and local hospital guidelines using physical examination, ultrasonography, X-ray, and computerized tomography (CT) scan as indicated. Any evidence of distant metastasis in the lung, liver, brain, and bone was recorded. Any event of mortality was documented, and the overall survival was calculated.

2.3. Statistical analysis

The associated clinical and pathological risk factors for progression into distant metastases were categorically compared using univariable and multivariable logistic regression analyses. Overall survival between different variables was analyzed using Kaplan-Meier curve and Log-rank (Mantel-Cox) tests. All statistical analyses were performed using the SPSS 17.0 software (SPSS Inc., Chicago). Statistically significant result was determined if P-value was less than 0.05.

3. Results

3.1. Patient clinical characteristics

The median age for patients with melanoma in this study (N = 82) was 62 years (range, 15–95 years) consisting of 63.4% (N = 52) females and 36.6% (N = 30) males. Among patients with CM (N = 45), 73.3% (N = 33) were CM and 26.7% (N = 12) were ALM. Patients with MM made up 45.1% (N = 37) of all patients. For CM, the most common locations were acral and extremities (93%, N = 42). All patients with CM (N = 45) were initially diagnosed with Breslow tumor thickness more than 4 mm (T4), 75.6% (N = 34) were positive for regional lymph nodes, 95.6% (N = 43) were with diameter more than 6 mm, 75.6% (N = 34) were at Stage III, and 46.7% (N = 21) were presented with ulceration. In MM, head and neck mucosa were the most prevalent sites (78.3%, N = 29), followed by gynecological mucosa (13.5%) and gastrointestinal mucosa (8.1%). For patients with MM (N = 37), 48.6% (N = 18) were with T4 lesions, 83.8% (N = 31) with diameter more than 6 mm, and 78.3% (N = 29) were diagnosed in the advanced stages. The demographic and clinical characteristics of patients with melanoma are summarized in Table 1.

3.2. Associated risks for the progression into distant metastasis

After median follow-up of 25 months, 33 patients (40.2%) had disease progression into distant organ metastasis. Proportions of the patients that developed distant metastasis were 44% (N = 20) with CM and 35.1% (N = 13) with MM. Single organ metastasis was found in 17 patients (51.5%) and multiple organ metastases were found in 16 patients (48.5%). The mean time of progression into distant metastasis was 13.2 months after surgical resection. The lung was the most common internal organ for distant metastasis from melanoma (45%, N = 15). Ulceration was the most significant risk for distant metastasis among all patients with melanoma (OR 7.181, 95% CI: 2.012–50.00, P = 0.05), Table 2. For specific organ metastasis, location of lesions in the acral and extremities was associated with more prevalent risk of lung metastasis (OR 7.181, 95% CI: 1.045–49.35, P = 0.045), nodular melanoma type was significantly associated with bone metastasis (OR 11.557, 95% CI: 1.442–92.61, P = 0.0021), and more female patients were associated with liver metastasis (OR 4.739, 95% CI: 1.00–10.7, P = 0.05), as shown in Table 3. No specific attributable risk factors were associated with distant metastases in the brain and the bone.
We also confirmed that melanoma in Asian patients often contributed to the general lack of public awareness about the disease. In contrast, 70% of primary melanosmas in Caucasians are diagnosed as superficial spreading CM and are located on the trunk and extremities [16]. Different from other Asian countries showing that ALM was the most common melanoma subtype (40–65% of total cases) [4,6], our study found that NM was the most common subtype (73%) followed by ALM (27%) and both subtypes were found in the acral and extremities. NM is commonly found in older patients in the head and neck regions with fast-growing and aggressive clinical course [3]. ALM has often been related with poorer prognosis compared to other types of CM [17] possibly due to the more advanced stages at diagnosis. However, another study found no significant difference in disease progression and overall survival between acral and non-acral cutaneous melanoma [18]. All CM in our study had Breslow T4, diameter more than 6 mm, and more than half were accompanied with ulceration (Table 1). CM among Asians are reported to be significantly thicker and are located in the acral with lesions prone to ulceration [4,15,19]. Although melanoma in children is very rare [20], our study also recorded an unusual nodular melanoma in a 15 years-old child that might need further analysis.

The distinct patterns of clinical presentations and the associated adverse risks of melanosmas might partly be due to the cytomorphological pathogenesis and the underlying genetic mutations. ALM and MM show more genetic aberrations in the somatic structural variants while CM demonstrate higher frequencies of small nucleotide variants and indels [8]. Patterns of actionable mutations including BRAF, NRAS, and CDKN2A are significantly different among CM, ALM, and MM although all of them show frequent mutations in the hTERT promoter [8]. MM are significantly associated with lower survival rates [9]. Although several driver mutations including BRAF and NRAS mutations are associated with aggressive behavior, the association of those mutations with worse prognosis are not clear in NM [8,21].

Melanoma is regarded as the most aggressive skin cancer due to its highly metastatic potential as well as its significant poorer prognosis. There were only a few studies that reported variables associated with progression into distant metastasis and the prognosis among melanoma patients from Asians particularly Indonesians. Several studies in melanoma demonstrated that the recurrent diseases were predominantly due to progression into distant metastases rather than locoregional recurrences [6,22]. Our study showed that ulceration was a risk factor of disease progression into distant metastasis (Table 2) confirming previous studies reporting that ulceration was associated with adverse prognosis in melanoma [6,23]. Ulceration indicated extensive skin structural destruction by the cancer cells that cannot be compensated for by the host response of reactive inflammation, fibrin closure, and hyperplasia of the adjacent epidermis. Lynph node infiltration in patients with melanoma has been associated with higher locoregional recurrence and distant metastases, as well as poor prognosis. In our study, however, no significant difference was found in the risk of progression into distant metastasis in patients with and without positive regional lymph node. The potential cause of this finding was the routine sentinel node biopsy was not performed in our hospital; hence occult lymph node infiltration will not always be detected. Sentinel lymph node biopsy is recommended in CM with Breslow thickness more than 1 mm (or more than 0.8 mm with ulceration) [13]. The SLNB is currently used to select patients who might benefit from adjuvant systemic treatments including immunotherapy or targeted BRAF inhibitors [13]. However, the SLNB practice has not been associated statistically with any significant difference in the disease-free survival and overall survival for both intermediate-thickness melanoma (1–4 mm) and thick melanoma (>4 mm), respectively [24]. The benefits and clinicopathological variables predictive of SLNB in acral and extremity melanoma have not been well characterized.

Among patients who progressed into distant metastasis, 45% of them were found in the lung with significant higher risk in ALM (OR 7.181, Table 3). The lung is the second most common internal organ for distant metastasis from melanoma in the first 3-year follow-up [25] because it receives the entire cardiac output from the extremities as well as most of

### Table 1
Clinical characteristics of melanoma patients and the comparison between cutaneous and mucosal melanomas.

| Variables | Melanoma (N = 82) | Cutaneous Melanoma (N = 45) | Mucosal melanoma (N = 37) |
|-----------|-----------------|-----------------|-----------------|
| Age category |                |                 |                 |
| <65       | 49 (60%)        | 23 (51%)        | 26 (70.3%)      |
| 65–75     | 17 (20.5%)      | 13 (29%)        | 4 (10.8%)       |
| >75       | 16 (19.5%)      | 9 (20%)         | 7 (18.9%)       |
| Sex       |                 |                 |                 |
| Male      | 30 (36.6%)      | 16 (35.6%)      | 14 (37.8%)      |
| Female    | 52 (63.4%)      | 29 (64.4%)      | 23 (62.2%)      |
| Histological subtype type | | | |
| NM        | 33 (40.2%)      | 33 (73.3%)      | 0 (0%)          |
| ALM       | 12 (14.6%)      | 12 (26.7%)      | 0 (0%)          |
| MM        | 42 (51.2%)      | 11 (24.4%)      | 31 (83.4%)      |
| Location |                 |                 |                 |
| Head/neck | 2 (2.4%)        | 2 (4.4%)        | 0 (0%)          |
| Trunk     | 1 (1.2%)        | 1 (2.2%)        | 0 (0%)          |
| Extremities | 29 (35.3%)  | 29 (64.4%)      | 0 (0%)          |

NM: nodular melanoma. ALM: acral lentiginous melanoma. MM: melanoma.

**3.3. Overall survival according to clinicopathological variables**

CM had shorter overall survival compared to MM (19.8 months and 23.4 months, respectively and P = 0.792). Positive regional lymph node was associated with shorter overall survival compared to those with negative regional lymph node (means of overall survival were 22.14 months and 28.19 months, respectively and Log-rank/Mantle-Cox test P = 0.05). Breslow T4 was associated with shorter overall survival compared to those with ≤4 mm (means of overall survival were 23.04 and 30.59 months, respectively and Log-rank/Mantle-Cox test P = 0.047). In subtype of nodular melanoma, Breslow T4 was also correlated with worse overall survival compared to those with ≤4 mm (means of overall survival were 19.4 and 31.2 months, respectively and Log-rank/Mantle-Cox test P = 0.006; Fig. 1). Other clinicopathological variables including clinical stage, age, sex, ulceration, and anatomic location were not significantly associated with overall survival.

**4. Discussion**

Our study highlighted that the majority of patients with melanoma were diagnosed in advanced stages with higher risks of relapse, recurrent metastatic disease, as well as poorer prognosis. The relatively low incidence of melanoma in Southeast Asia including Indonesia might contribute to the general lack of public awareness about the disease [15]. We also confirmed that melanoma in Asian patients often presented as MM and ALM and the predominant sites of skin lesions were in the acral of extremities (Table 1).
### Table 2
Odds ratios and 95% confidence intervals of different clinicopathological variables to the risk of progression into distant metastasis using univariable and multivariable logistic regression.

| Variables      | Category       | Melanoma (total) | Cutaneous melanoma | Mucosal melanoma |
|----------------|----------------|------------------|--------------------|-----------------|
|                |                | OR (95%CI) P value | OR (95%CI) P value | OR (95%CI) P value |
|                | Univariate     | Multivariate     | Univariate         | Multivariate    |
|                |                |                  | Univariate         | Multivariate    |
|                |                |                  | Univariate         | Multivariate    |
|                |                |                  | Univariate         | Multivariate    |
| Age (years)    |                |                  |                    |                 |
| ≤65            | ref            | 0.463 (0.308-1.888) | 0.708 (0.245-2.047) | 0.524           |
| >65            | 0.762          | 0.497 (0.148-1.664) | 0.257 (0.461-2.017) | 0.304           |
| Sex            | Male           | 0.578 (0.196-1.521) | 2.105 (0.609-7.246) | 0.996 (0.052-1.229) |
|                | Female         | ref              | ref                | ref             |
| Histological type | Nodular | 0.938 (0.342-3.468) | 0.866 (0.086-2.964) | 0.448           |
|                | Other          | ref              | ref                | ref             |
| Breslow thickness | >4 mm | 1.067 (0.398-2.858) | 2.557 (0.277-28.747) | 0.447           |
|                | ≤4 mm          | 0.503 (0.373-4.567) | ref                | ref             |
| Node           | Positive       | 0.684 (0.288-5.309) | 0.775 (0.190-6.957) | 2.702 (0.602-12.048) |
|                | Negative       | ref              | ref                | ref             |
| Ulceration     | Yes            | 0.08 (1.745-25.6) | 10.00 (2.012-50.00) | 0.005 (0.613-8.587) |
|                | No             | ref              | ref                | ref             |
| Stage (AJCC VIII) | Early (I-II) | ref              | ref                | ref             |
|                | Advanced (III) | 0.85 (0.114-2.286) | 0.510 (0.242-3.715) | 0.938           |
| Location       | Acral, extremities | 0.346 (0.625-11.656) | 0.185 (0.139-19.654) | 0.782           |
|                | Trunk, head and neck | ref            | ref                | ref             |
| Diameter       | ≤6 mm          | 2.844 (0.304-26.657) | ref                | ref             |
|                | >6 mm          | 0.663 (0.370-69.827) | ref                | ref             |

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the lymphatic drainage that enters the venous system through the first capillary plexus [26]. Acral melanoma has a propensity to infiltrate the venous system which has direct drainage from the inferior vena cava to the lungs as well as lymphatic drainage to the brachiocephalic vein [26]. The bone is also a common site of distant metastasis from advanced stages of melanoma usually with multiple metastases [27]. However, no study other than this one has previously reported the predilection of bone metastasis from the specific type of NM. The attributed factors for bone metastasis from melanoma are commonly associated with thicker Breslow depth, regional lymph node involvement, and other sites of

Table 3

| Variables             | Pulmonary metastasis | Pleural metastasis | Bone metastasis | Liver metastasis | Brain metastasis |
|-----------------------|----------------------|--------------------|-----------------|-----------------|-----------------|
|                       | Category             | OR (95%CI)         | P value         | OR (95%CI)      | P value         | OR (95%CI)      | P value         | OR (95%CI)      | P value         | OR (95%CI)      | P value         |
| Age (years)           | ≤65 ref              |                    |                 | ref (0.983      | 0.05 ref        | ref             |                 | ref             |                 | ref             |                 |
|                       | >65 0.463            | (0.117–1.182)      | 0.271           | 1.677 (0.442–6.354) | 0.447           | 1.020 (0.165–6.290) | 0.983           | 0.05 (0.010–1.002) | –               | –               |
| Sex                   | Male 0.795           | (0.218–2.896)      | 0.728           | 0.580 (0.159–2.113) | 0.409           | 0.602 (0.129–2.806) | 0.518           | 0.211 (0.044–1.000) | 0.05             | –               |
|                       | Female ref           | ref                |                 | ref             | ref             | ref             |                 | ref             | ref             | ref             |                 |
| Histological type     | Nodular 0.709        | (0.152–3.301)      | 0.661           | 0.360 (0.084–1.543) | 0.169           | 11.557 (1.442–92.608) | 0.021           | 5.236 (0.726–37.76) | 0.101            | 1.414 (0.040–50.26) | 0.849           |
|                       | Other ref            | ref                |                 | ref             | ref             | ref             |                 | ref             | ref             | ref             | ref             |
| Breslow thickness     | >4 mm 0.505 (0.087–2.916) | ref                  | 0.503           | 2.119 (0.421–10.670) | 0.363           | 6.806 (0.824–56.206) | 0.075           | 2.531 (0.393–16.292) | 0.328            | 0.267 (0.009–7.600) | 0.440           |
|                       | ≤4 mm ref            | ref                |                 | ref             | ref             | ref             |                 | ref             | ref             | ref             | ref             |
| Node                  | Positive 3.199 (0.461–22.217) | 0.240              | 0.489           | (0.078–3.072) | 0.446           | 0.094 (0.004–2.083) | 0.135           | 2.010 (0.242–16.717) | 0.518            | –               | –               |
|                       | Negative ref         | ref                |                 | ref             | ref             | ref             |                 | ref             | ref             | ref             | ref             |
| Ulceration            | Yes 3.257 (0.746–14.084) | 0.116              | 0.480           | (0.097–2.384) | 0.370           | –                | –                | –                | 16.95 (1.379–200) | 0.027           | 4.100 (0.204–82.53) | 0.357           |
|                       | No ref               | ref                |                 | ref             | ref             | ref             | ref             | ref             | ref             | ref             | ref             |
| Stage (AJCC VIII)     | Early (I-II) ref     | ref                |                 | ref             | ref             | ref             |                 | ref             | ref             | ref             | ref             |
|                       | Advanced (III) 0.247 | (0.035–1.730)      | 0.159           | 0.532 (0.086–3.313) | 0.499           | 5.686 (0.186–173.907) | 0.319           | 0.269 (0.022–3.276) | 0.269            | –               | –               |
| Location              | Acral, extremities   | 7.181 (1.045–49.35) | 0.045           | 3.855 (0.615–24.186) | 0.150           | 0.527 (0.038–7.248) | 0.632           | 0.349 (0.029–4.121) | 0.349            | –               | –               |
|                       | Trunk, head and neck ref | ref            |                 | ref             | ref             | ref             |                 | ref             | ref             | ref             | ref             |

Fig. 1. Association of lymph node status and Breslow depth with worse prognosis in melanoma patients. (A) Tumor infiltration to the regional lymph nodes were associated with shorter overall survival (means were 22.14 and 28.19 months in positive and negative regional lymph nodes, respectively; Log-rank Mantel-Cox test, \( P = 0.001 \)). (B) Breslow thickness more than 4 mm was associated with worse overall survival (means were 23.04 and 30.59 months in T4 and T1-3, respectively; Log-rank Mantel-Cox test, \( P = 0.047 \)). (C) In nodular melanoma, Breslow thickness more than 4 mm was associated with worse overall survival (means were 19.4 and 31.2 months in T4 and T1-3, respectively; Log-rank Mantel-Cox test, \( P = 0.006 \)).
surveillance every 3
specifically for high-risk patients with mucosal, nodular, and acral
melanomas. The generally accepted guidance is thorough and regular
surveillance also needs to be performed. There are no universally
accepted guidelines for surveillance after complete surgery resection
as an effective test to assess skin lesions with an ability of magnification
to regional lymph nodes and Breslow T4 were signifi-
cantly associated with shorter survival in our study. The delayed
detection as also shown in other more common cancer [31–32] might
counter to advanced disease at presentation as well as poorer
survival rates than patients from other Asian countries [6,15]. There-
fore, increasing public health education and awareness of potential skin
or mucosal lesion as melanoma is very crucial in Indonesia to reduce
delayed diagnosis of melanoma. With the relatively low median survival
of patients with melanoma in our study and other studies from Indonesia
(19 months compared to 3–4 years in China and Japan), improvements
of standard of care including diagnosis, referral system, and treatment of
melanoma must be effectively performed in Indonesia. It has been also
reported that many patients with melanoma from Asia receive only
palliative treatment primarily because of too advanced disease and
limited options of available treatment [6]. Although surgical resection is
the backbone of melanoma treatment, adequate margin-free resection
particularly in advanced stages and in MM, this is not always possible.
Neoadjuvant therapy in bulky tumors, late stages, and with locoregional
metastasis has been currently recommended to aid surgical resection
and improve survival [34,35]. Immunotherapy using PD-1, PD-L1, and
CTLA-4 inhibitors has been shown clinically to be very effective for
high-risk and inoperable melanomas to improve survival and quality of
life [12]. However, the immune checkpoint inhibitors are not yet covered
by the national insurance in Indonesia. Accordingly, more
engagement with the health policy makers, insurance company, and
medical industry is also required to raise and improve access to these
novel and effective therapies.

Improvement of diagnostic strategies to early detect melanoma is
very important to increase the chance of complete resection. In addition
to careful physical examination of a suspicious skin lesion and confir-
mation with histology examination, dermatoscopy has been considered
as an effective test to assess skin lesions with an ability of magnification
into 6–100 times [36]. Better visualization of raw structures and pat-
terns of skin lesions can be achieved using dermatoscopy [36]. The
digital images can be stored and potentially processed using current
artificial intelligence to improve diagnosis as well as monitoring of
disease progression [36]. In addition to early detection, improvement of
surveillance also needs to be performed. There are no universally
accepted guidelines for surveillance after complete surgery resection
specifically for high-risk patients with mucosal, nodular, and acral
melanomas. The generally accepted guidance is thorough and regular
skin and lymph node examinations to detect both disease recurrence and
new primary tumor. NCCN guidelines have recommended for structured
surveillance every 3–6 months for the first 3 years followed with 4–12
months for an additional 2 years [37]. Extension of structured follow-up
after 5 years is not specifically recommended [37]. Adjustment of sur-
veillance particularly for patients with high-risk melanomas including
those with ulceration, thicker Breslow tumor depth, and positive
involvement of lymph nodes might also be required [13].

The prime strength of this study is the elucidation of factors
associated with progression into distant metastasis and overall survival
from high-risk patients with melanoma of Asian patients predominantly
diagnosed as nodular, acral lentiginous and mucosal melanomas. Limita-
tions of this study are those that are naturally due to the retrospective
design. In addition, the degree of excessive ulceration and type of
infiltrative or attenuative ulceration were not differentiated. Longer
follow-up and incorporation of histological and molecular biomarkers
including BRAF, NRAS mutations, and PD-L1 [12] expression are
required in the future study for planning of further advanced treatment
and prognostic determination.

5. Conclusion

Our findings show that although melanoma is not a common cancer in
Indonesia, most patients are diagnosed in advanced stages with higher
risks of relapse, disease progression, as well as poor prognosis. Easing
and facilitating the referral health system for diagnosis and treatment of
melanoma is also required to prevent delayed diagnosis and treatment.
Future studies should elucidate the clinical course, risk factors for
relapse and worse survival, while identifying underlying actionable
mutations and gene rearrangements, with more routine follow-up of
responses to treatment, in addition to tailoring a more comprehensive
surveillance system in Asian/Indonesian patients with melanoma.

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Ethical approval

The study has been conducted following ethical principles and the
protocol has been approved by the Ethics Committee of the Faculty of
Medicine, Public Health, and Nursing - Universitas Gadjah Mada
Yogyakarta (KE/0939/09/2020).

Consent

Written informed consent was obtained from the participants. Pa-

tient identifying related material was not used in this manuscript.

Author contribution

SLA and TA conceived the study. SLA, RC, HYB collected and
analyzed the data. SLA wrote the first draft with critical feedback from
WAH and TA. All authors agreed on the final version of the manuscript
draft.

Registration of research studies

The study has been registered in the ResearchRegistry with identi-
fication number researchregistry6192. Please find in the https://www.
researchregistry.com/browse-the-registry#home/registrationdeta-

ils/S59de96dc4597c0015c1a5f8/.

Guarantor

SLA, Universitas Gadjah Mada.

Declaration of competing interest

We declare that no potential conflict of interest exists.
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A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amjms.2020.12.004.

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