



Clinical significance of histologic subtyping of malignant pleural mesothelioma

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Abstract: Malignant mesothelioma (MM) is uncommon, but very aggressive tumor arising from the mesothelial cells of pleura, pericardium, peritoneum, and tunica vaginalis. Despite multimodality treatments 5-year survival is only 5% after the diagnosis. Histology and TNM staging system are still the best prognostic factors. Furthermore, histologic subtype of MM determines the clinical management of the patients. According to the 2015 WHO classification, MM is divided into diffuse, localized and well differentiated papillary mesothelioma. Major histologic subtypes of diffuse MM, namely epithelioid, biphasic and sarcomatoid, have different prognosis. However, in the last decade it has become evident that more detailed subclassification and histologic/cytological characterization of MM have prognostic and perhaps predictive implications. In this review, major histologic subtypes and cytological features of MM are presented and their relation with prognosis and predictive biomarkers is discussed.

Keywords: Malignant mesothelioma (MM); epithelioid malignant mesothelioma; biphasic malignant mesothelioma; sarcomatoid malignant mesothelioma (SMM); histology

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Introduction

Malignant mesothelioma (MM) is a rare and, in majority of cases, highly aggressive tumor. It arises from the mesothelial cells lining serous cavities (pleura, pericardium, peritoneum, and tunica vaginalis). In Western countries, incidence of MM is still slowly increasing, and should be reaching its peak in this decade (1-5). Without treatment, median survival is 7 to 9 months, and even with treatment it is no more than 22 months (6). Despite advances in multimodality treatment options (7-9), 5-year-survival is only 5% (10,11).

The histologic subtype of MM and TNM stage remain the major prognostic factors (12). It is well known that epithelioid subtype is associated with better prognosis when

compared to sarcomatoid and biphasic subtypes (13). The patients with epithelioid mesothelioma may benefit from surgical treatment, while the patients with sarcomatoid mesothelioma do not show the same benefit and therefore are not subjected to surgery. Furthermore, the epithelioid subtype shows a large spectrum of morphological heterogeneity that is nicely described and illustrated in the 2015 WHO classification (13). Recently published studies demonstrated that morphological subtype of epithelioid mesothelioma does have an impact on outcome (14-16). On the other hand, in biphasic mesothelioma the proportion of sarcomatoid component seems to be the major driver of prognosis (17,18). These are just a few examples of how morphology may have an impact on prognosis and treatment decision. It remains to be determined how

many details in regards to morphology of MMs have to be mentioned in the diagnostic pathology reports. In addition to architecture of mesothelial subtypes, recent studies indicate that cytologic features, mitoses and necrosis may be translated into grading score that also has prognostic significance (19,20). Currently there is no recommendation on grading of epithelioid mesotheliomas, but that may change in the near future.

In contrast to other tumor types such as lung cancer, MMs show rather a limited number of genomic alterations and usually lack of druggable targets. Recent developments in immunotherapy for MMs suggest that histology may be predictor of response. Therefore, it remains to be seen if precise histological subtyping and grading of mesothelioma would be of any predictive value for novel non-surgical therapeutic approaches.

In this review, major histologic subtypes and cytological features of MM are presented and their relation to prognosis and possible predictive value is discussed.

Well-differentiated papillary mesothelioma (WDPM)

WDPM is a localized or multifocal tumor. It is exceptionally rare in pleura, and occurs more often in peritoneum and tunica vaginalis testis (21,22). Histologically, it is defined by papillary growth pattern, where one layer of cytologically bland, epithelioid cells covers papillae. Fibrovascular cores of papillae often show myxoid changes. Atypia and mitoses are absent. WDPM most commonly grows superficially. In rare cases, focal and superficial invasion can be present as a stalk invasion with bland-looking cells or presenting as solid aggregates with cytological higher grade. In such case, term "WDPM with invasive foci" is applied and closer follow-up due to recurrence is needed (23).

Few molecular studies published up to date demonstrated *NF2* heterozygous deletion, *E2F1* point mutation and one case of germline *BAP1* mutation (24-26), characterizing WDPM as a neoplastic process. Recently, Stevers *et al.* showed that peritoneal WDPM harbors mutually exclusive somatic missense mutations in *TRAF7* or *CDC42* genes, while no alterations in *BAP1*, *NF2*, *CDKN2A*, *DDX3X*, *SETD2*, and *ALK* genes have been found (27). Since the prognosis is very good, with occasional local recurrences, differentiation from diffuse epithelioid MM with predominant papillary pattern is crucial. The main characteristic features favoring WDPM are monomorphic

histological presentation with only one (papillary) pattern, single layer of cells, low mitotic count, and absence of atypia and invasion. WDPM has intact *BAP1* nuclear expression, and no homozygous deletion of *CDKN2A/p16*, therefore these features can be helpful in the differential diagnosis with diffuse MM. Reactive mesothelial proliferation is another diagnostic pitfall, however it is characterized by thinner papillae and hyalinized fibrovascular cores with prominent blood vessels. In this differential diagnostic situation morphology trumpets over ancillary methods. Radiologic correlation is always needed, and the diagnosis on a small biopsy is often challenging.

Localized malignant mesothelioma (LMM)

LMM is defined as a solitary, nodular lesion, without diffuse involvement of the serosal surface, both macroscopically and histologically. Thorough radiological investigations and thoracoscopic inspection is necessary to be able to confirm the diagnosis of LMM. It presents in 3 histologic types: epithelioid, sarcomatoid and biphasic (28,29). Genetically they are heterogeneous, and some have *BAP-1* mutations like DMM, but others have mutations, like *TRAF7*, which are more specific for LMM (30).

Although LMM is very rare, it has to be recognized, as the prognosis of this unique type is much better than for diffuse MM, and it is potentially curable by complete surgical excision (28,31).

Diffuse malignant mesothelioma (DMM)

DMM is according to the 2015 WHO classification divided in epithelioid, sarcomatoid and biphasic subtypes (*Figure 1*) (13). Importance of its recognition lies in the fact that the overall prognosis of the patients with DMM is very poor, even when compared to LMM, and especially to WDPM. Major diagnostic challenges are in the recognition of reactive lesions, recently described in-situ mesotheliomas and in differentiation from the most important differential diagnostic possibilities, such as carcinomas and spindle cell lesions/sarcomas. Diagnosis relies on morphological criteria, as well as on immunohistochemistry, and sometimes even molecular analyses is needed. However, it is out of the scope of this review to go into this problematic diagnostic challenges. In the next paragraphs, we will shortly explain the importance of recognizing specific histologic types and additional cytological and stromal features.

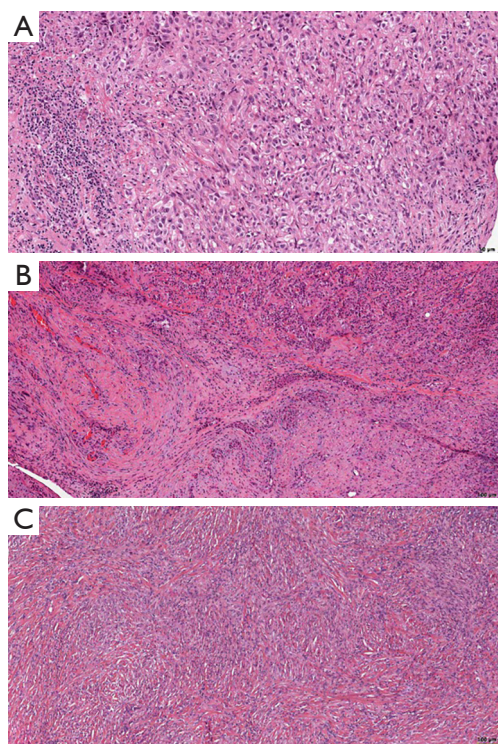


Figure 1 Histologic presentation of 3 major malignant mesothelioma types; epithelioid (A), biphasic (B) and sarcomatoid (C). (H&E staining; A: objective $\times 10$, B and C: objective $\times 5$).

Epithelioid malignant mesothelioma (EMM)

EMM, found in up to 80% of patients with MM, is characterized by diffuse and invasive growth of epithelioid cells from pleural surface. It has been known for its heterogeneous morphology. According to the 2015 WHO Classification, patterns that occur more often are solid, tubulopapillary, and trabecular, followed by micropapillary, adenomatoid, clear cell, transitional, deciduoid, and small cell (13). Furthermore, EMM usually has more than two growth patterns, and this feature can be used as a diagnostic criterion versus some other malignant tumors. Recognition of different growth pattern is important since distinct subtypes have prognostic importance. In a study by Kadota *et al.* (14) trabecular and tubulopapillary pattern proved to be favorable prognostic patterns, in comparison to other patterns in EMM. The same was true for the myxoid and microcystic pattern in another study (15). In contrast, pleomorphic pattern was found to be associated with poor survival, more similar to the patients with sarcomatoid malignant mesothelioma (SMM) (14,16,32). Pleomorphic characteristic can also occur in SMM (33). Recently

described transitional pattern is characterized by sheets of round to oval malignant mesothelial cells with abundant cytoplasm, morphologically lying between epithelioid and spindle cells (17,34). It is associated with a survival similar to that of the sarcomatoid and pleomorphic types. Furthermore, molecular characteristics are also similar to SMM (Galateau Salle F *et al.*, 2020, submitted for publication). Some authors regarded lymphohistiocytoid mesothelioma as a separate, uncommon subtype of SMM (35), while others, based on a better prognosis, considered this pattern as a part of the epithelioid subtype (36). Of note, a very small number of lymphohistiocytoid mesothelioma cases has been reported in the literature, sometimes with better, and sometimes with worse survival data (37). The similar problem of (under) representativeness have another three mesothelioma types/patterns, namely deciduoid mesothelioma, signet ring and small cell mesothelioma. All of them are extremely rare, and it is difficult to define them, in a sense of avoiding misdiagnosis and providing adequate diagnostic reproducibility. Deciduoid type was first described in 1985 by Talerman *et al.* (38) in the peritoneum, and later in the pleura. However, less than 50 cases of pleural deciduoid mesotheliomas have been published up to date, and prognosis is closer to EMM than to sarcomatoid one (39). Small cell variant of MM is rarer, first reported in series of 13 cases by Mayal and Gibbs in 1992 (40), characterized by similar cell morphology to SCLC, but different immunohistochemical profile (negative for carcinoma markers, as well as chromogranin and synaptophysin, positive for mesothelial markers, and occasionally and focally for CD56). The prognosis is poor, with reported mean survival of 8.2 months (41). Signet ring cell variant seems to be even rarer than previous two variants, with so far less than 30 reported cases, majority involving the pleura (42). Median survival was 15 months (43), and the major diagnostic challenge is ruling out the metastasis.

In the recently published EURACAN/IASLC proposal for histologic classification of pleural mesothelioma (44), consensus was made to report the following histologic patterns: tubular, papillary, tubulopapillary, trabecular, solid, micropapillary, adenomatoid, microcystic, pleomorphic and transitional (*Figures 2,3*). These patterns should be reported in percentages in the resected specimens, and mentioned in the report of smaller samples. Other characteristics, such as rhabdoid, deciduoid, small cell, clear cell, signet ring cell and lymphohistiocytoid, are classified as cytological features, and should be reported as such (*Figure 4*). Myxoid

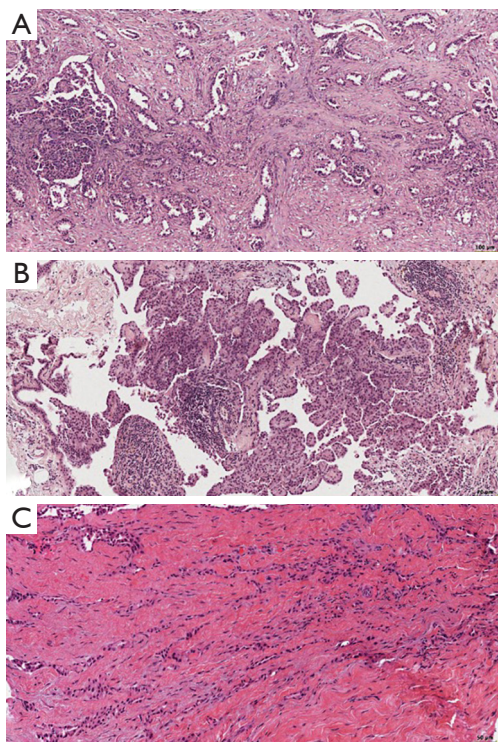


Figure 2 Representative images of tubular (A), tubulopapillary (B) and trabecular pattern (C). (H&E staining; A: objective $\times 5$, B and C: objective $\times 10$).

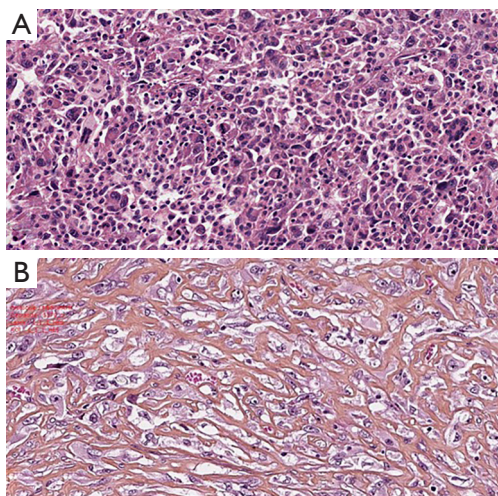


Figure 3 Presentation of pleomorphic (A) and transitional (B) patterns. (H&E staining; A,B: objective $\times 20$; B: by courtesy of Françoise Galateau Salle).

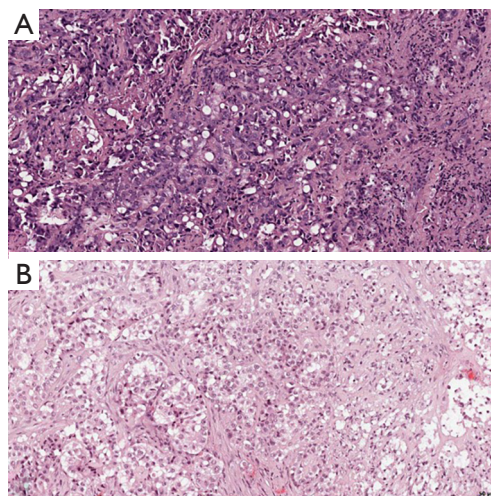


Figure 4 Histologic images of rare cytologic features; signet ring cells (A) and clear cells (B). (H&E staining; objective $\times 5$).

stroma should be reported in EMM when present in more than 50% of tumor, in which less than 50% of tumor cells grow in a solid growth pattern, while it is a favorable prognostic factor.

SMM

SMM is defined by diffuse and infiltrative growth of spindle cells, or mesenchymal appearing cells. A special subtype, with at least 50% of tumor mass composed of dense hyalinized stroma that is interspersed between malignant mesothelial cells, is called desmoplastic malignant mesothelioma (13). SMM and desmoplastic MM are very rare, comprising less than 10%, and less than 2%, of all mesothelioma patients, respectively (13). In contrast to other MM, SMM and desmoplastic subtype usually present without pleural effusion, and often have more distant metastases. The latter is especially true for desmoplastic MM, in which distant metastases might occur in up to 60% of patients (45). Both are very challenging for diagnosis, especially in a small biopsy specimen, and major differential diagnosis includes sarcomas (for SMM) and fibrosing pleuritis (for desmoplastic malignant mesothelioma). Pronounced atypia of tumor cells, necrosis and clear invasion are helpful for the diagnosis. The tumor cells

can show a wide range of atypia, varying from minimal to severe, with pleomorphic features like atypical giant cells, bizarre nuclei, with presence of atypical mitotic figures. Furthermore, usual mesothelial immunohistochemical markers in these tumors may not be helpful. Tumor cells usually stain for cytokeratins, and GATA 3 shows strong nuclear staining (46). However, the right diagnosis is very important for the evaluation of prognosis and adequate treatment decision. Klebe *et al.* (47) suggested a separate subtype of mesothelioma with heterologous elements (osteosarcomatous, chondrosarcomatous, rhabdomyosarcomatous and rarely liposarcomatous). They presented 27 mesotheliomas with heterologous elements, 16 were SMM, 10 BMM and 1 diagnosed as EMM (in a small biopsy). Their prognosis proved to be very poor, with median survival of 6 months, and only 1 patient survived longer than 1 year (47). In the literature, there are some reports of very long survival of these patients, one reaching even 69 months (48,49). However, heterologous elements occur extremely rare, in less than 0.5% of all MM, and the consensus proposal of EURACAN/IASLC included these element as stromal features, together with desmoplastic stroma (44).

Prognosis is extremely poor- untreated patients with SMM die of disease within 5–6 months, and majority of patients with desmoplastic malignant mesothelioma have similar or slightly shorter survival time (12,50,51). As mentioned previously, published data clearly demonstrate similar survival of patients with pleomorphic and transitional patterns, however, due to small number of patients and published studies, they are still included both under EMM and SMM (44).

Biphasic malignant mesothelioma (BMM)

BMM is characterized by having at least 10% of each, epithelioid and sarcomatoid component. It comprises 10–15% of all DMM, and prognosis lies between pure epithelioid and sarcomatoid MM (13). Some authors suggest that the amount of sarcomatoid elements is crucial for prognosis. It is known that patients with EMM might profit from surgical procedures, while SMM have very poor prognosis and surgery does not improve survival. Because of these features, it is logical to presume that the amount of epithelioid part in BMM has prognostic role, and therefore influence therapy decisions. However, studies analyzing this are rare, and differ in the proposed cut-off values (17,18). Vigneswaran *et al.* demonstrated

that patients with less than 50% of epithelioid component have very poor survival (6.62 months) in comparison to patients with more than 50% (11.8 months) or patients with pure EMM (20.1 months). Epithelioid component in that study was independent predictor of survival (18). Experts of the French Mesothelioma Panel found better overall survival in patients with more than 20% of epithelioid component. Another study performed by the International Mesothelioma Panel, showed how difficult it is to recognize BMM, reaching only moderate interobserver agreement in diagnosis (weighted kappa value of 0.45) (17). The main problem was identification of a spindle cell component as malignant. BAP1 loss, and *CDKN2A/p16* homozygous deletion were in these instances helpful. Furthermore, grading of the spindle cell component, may have prognostic significance. Additionally, the importance of cytokeratin staining in diagnosing BMM was also demonstrated (17). It is known that the accuracy of histologic classification made on small samples is not ideal, and concordance with diagnosis of surgical resection is in range from 72–83% (52,53). Especially underdiagnosed in small biopsies are BMM, while EMM are overdiagnosed. One reason is definitely the sampling issue, and another is strict criteria of 10% of either component. According to the EURACAN/IASLC proposal for histologic classification of pleural mesothelioma consensus paper, definition for BMM should be changed in a way that it can be diagnosed in small samples even without reaching currently set cut-off values of 10% (44).

Biomarker testing in MM

Currently, there is no routinely used testing for prognostic or predictive biomarkers for MM. Emerging data suggest that the histologic type of mesothelioma show different associations with different predictive biomarkers.

PD-L1 is very interesting, since it is used also as a predictive biomarker for immunotherapy, which is now standard therapy for many different solid tumors. In published studies, PD-L1 expression was related to poor prognosis in MM patients (54–58). In a study by Nguyen *et al.* the difference in median survival of MM patients, depending on PD-L1 expression and regardless of histology, was 9.5 months in favor of negative PD-L1 expression (58). Their study, as well as other studies, showed also that PD-L1 expression is associated with SMM (57,59).

The same was confirmed by the one of the largest study so far, using 214 samples of MAPS phase 3 randomized

trial (60). Thirty-five point nine percent [77] samples were PD-L1 positive, out of those 35.1% (27 samples) had 50% or more positive tumor cells. SMM and BMM were also here more often positive. In analysis of PD-L1 expression and overall survival (OS) they showed that patients with lower PD-L1 expression (using both 1% and 50% as a cut-offs) have better OS. However, after multivariate analyses, and adjusting for histology, performance status, smoking and treatment arm, this was no longer statistically significant. This raises the question whether PD-L1 positivity is just a surrogate marker for SMM, which could explain its association with worse prognosis.

Another important question is can PD-L1 expression in MM be used as a predictive biomarker for immunotherapy. Retrospective study by Rivalland (61) on a very small group of patients showed better objective response rate (ORR) was associated with higher PD-L1 expression. Applying cut-off of 5% for PD-L1 positivity, ORR was 40%, increasing to 50% when cut-off of 50% was applied. In PD-L1 negative patients, ORR was 22%. Although there are ongoing trials evaluating immunotherapy in a second and third line settings, with relation to PD-L1 expression, MAPS2 randomized non-comparative phase 2 trial showed improved objective response and disease control rates in patients expressing PD-L1 both with 1% and 25% used as a cut-off (62). In many clinical trials where there was obvious clinical benefit of immunotherapy, it was regardless of PD-L1 expression (63-66). Only one study of nivolumab and ipilimumab showed tendency of greater benefit for PD-L1 positive patients, however the study cohort was very small (only 34 patients). Like in other solid tumor types, there are many issues with PD-L1 testing: different antibody clones, which are similar but not the same, different cut-off values used in different studies, and tumoral and spatial heterogeneity. This results in different percentages of positive MM samples, ranging from 18% to 72% (54-59,67). Furthermore, it might also explain (lack of) correlation with the response to immunotherapy. Brosseau study also failed to demonstrate predictive significance of PD-L1 expression for bevacizumab-pemetrexed/cisplatin therapy. Interestingly, when analyzing only EMM patients, and using 50% as a cut-off for PD-L1 positivity, they showed a non-significant trend: patients with PD-L1 expression <50% demonstrated overall survival (OS) of 23 months in comparison to 12.3 months in a group where PD-L1 was present in 50% or more tumor cells. However, using the same cut-off for progression free survival (PFS) analyses, PD-L1 proved to be significant and independent prognostic

factor (aHR 2.16; 95 CI, 1.2-3.84; P=0.0087); PD-L1 positive tumors showed 6.7 months of median PFS versus 9.9 months in low expression or negative group (60).

Another promising predictive biomarker is mesothelin, a membrane antigen, highly expressed in EMM and used as a target for new therapies (68,69). Drug-conjugated antibody against mesothelin, anatumab ravtansine, in a phase II study failed to show better progression free survival or OS in comparison to vinorelbine, as a second-line therapy (70). On the other hand, immunotoxin SS1P composed of anti-mesothelin antibody and pseudomonas exotoxin, in a phase I study, induced partial response in 77% of patients, although there were only 12 patients involved in this phase (71). Furthermore, application of a chimeric anti-mesothelin monoclonal antibody, amatuximab, with standard chemotherapy as a first line therapy, induced disease control rates of 90% (72). Innovative approach combining mesothelin expression and immunotherapy includes chimeric antigen receptor T cells (CAR-T) modified in a way to bind with tumor cells expressing mesothelin, and stimulating T cells to destroy them, and is currently in early phase clinical studies (73). Unfortunately, mesothelin is not expressed in SMM, so all mentioned above relates only to EMM. It seems that the SMM may respond to arginine deprivation therapy. Argininosuccinate synthetase 1 (ASS1) is the enzyme limiting arginine production, and is associated with increased tumorigenesis and more aggressive disease. In a phase I study, arginine depletion agent ADI-PEG 20 (PEGylated arginine deiminase) was applied with standard-of-care chemotherapy in nine ASS1-deficient patients (proven by immunohistochemistry), among whom were 5 patients with MM (74). Seven patients demonstrated partial response, including 3 with SMM or BMM, and all of the patients had stable disease. Based on this results, patients with ASS1 loss in 75% of tumor were included in a phase II/III study whose results should be soon published (75)

It has been known that BAP-1 loss detected by immunohistochemistry is used as a proof of malignancy, and therefore in differentiation of reactive mesothelial proliferation versus MM (76-81). BAP1 is frequently lost in epithelioid diffuse MM in contrast to sarcomatoid mesothelioma. Furthermore, BAP1 loss induces enhancer of zeste homologue 2 (EZH2)-dependent transformation increasing trimethylated histone H3 lysine 27 (H3K27me3) and repressing polycomb repressive complex 2 (PRC2), inducing mesothelial proliferation, migration, and tumorigenesis (82,83) Inhibition of EZH2

in MM with BAP1 loss induced apoptosis and prevented tumor formation (82). EZH2 inhibitor, tazemetostat, is investigated in a phase II clinical study in MM patients (NCT02860286).

Conclusions

In this review, we have demonstrated well known diversity in histologic presentations of MMs that have prognostic significance and impact on treatment decisions. A correlation between morphology of malignant mesothelioma and predictive biomarkers is still in the development, and large clinical trials may give us the answers that would guide pathology practice and biomarker testing in this fatal disease.

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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