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External multicentre validation of pseudomyxoma peritonei PSOGI-Ki67 classification

A. Arjona-Sanchez [a, b, *, 1], A. Martinez-López [a, c, 1], M.T. Moreno-Montilla [b], J. Mulsow [d], P. Lozano-Lominchar [e], B. Martínez-Torres [f], B. Rau [g], E. Canbay [h], A. Sommariva [i], M. Milione [j], M. Deraco [k], O. Sgarbura [l], A. Torgunrud [m], V. Kapenekian [n], N.J. Carr [o], A. Hoorens [p], J.B. Delhorme [q], R. Wernert [r], D. Goere [s], L. Martin-Roman [d], S. Cosyns [t], K. Flatmark [u], B. Davidson [v], L. Khellaf [w], F. Pereira-Perez [f], L. Rodriguez-Ortiz [b, s], A. Ibáñez-Costa [b], A. Romero-Ruiz [b, **], On behalf of EuroPMP COST action and GECOP group

[a] *Unit of Surgical Oncology, Department of Surgery, Reina Sofia University Hospital, Spain*
[b] *Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, University of Cordoba, Cordoba, Spain*
[c] *Pathology Unit, Reina Sofia University Hospital, Spain*
[d] *National Centre for Peritoneal Malignancy, Mater Hospital, Dublin, Ireland*
[e] *Department of General Surgery, Peritoneal Carcinomatosis, Sarcoma and Complex Pelvis Cases, Hospital General Universitario Gregorio Marañon, Madrid, Spain*
[f] *Department of General Surgery, Hospital University Fuenlabrada, Madrid, Spain*
[g] *Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität, Department of Special Surgical Oncology, Berlin, Germany*
[h] *NPO HIPEC Istanbul centre for Peritoneal Surface Malignancies, Istambul, Turkey*
[i] *Advanced Surgical Oncology Unit Surgical Oncology of the Esophagus and Digestive Tract, Veneto Institute of Oncology IOV-IRCCS Padova, Italy*
[j] *Pathology Division, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[k] *Peritoneal Surfaces Malignance Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[l] *Department of Surgical Oncology, Cancer Institute of Montpellier, University of Montpellier, IRCM, Institut de Recherche en Cancérologie de Montpellier, Université de Montpellier, Institut régional du Cancer de Montpellier, Montpellier, France*
[m] *Department of Tumor Biology, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway*
[n] *Unit of Surgery, Hospitaux du Lyon, France*
[o] *Pathology Department, Peritoneal Malignancy Institute Basingstoke, UK*
[p] *Department of Pathology, Ghent University Hospital, Ghent, Belgium*
[q] *Department of general and digestive surgery, Hautepierre Hospital, Hôpitaux universitaires de Strasbourg, France*
[r] *Surgical Oncology, ICO Paul Papin, Angers, France*
[s] *Digestive Surgery, APHP Hopital Saint Louis, France*
[t] *Department of Human Structure and Repair, Ghent University, Ghent, Belgium*
[u] *Department of Gastorenterological Surgery, The Norwegian Radium Hospital, Oslo university Hospital, Oslo, Norway*
[v] *Department of Pathology, The Norwegian Radium Hospital, Oslo university Hospital, Oslo Norway. University of Oslo, Faculty of Medicine, Institute of Clinical Medicine, N-0316, Oslo, Norway*
[w] *Department of Pathology, Cancer Institute of Montpellier, University of Montpellier, Montpellier, France*

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ABSTRACT

Background: Pseudomyxoma peritonei (PMP) is a rare malignant disease. Adding of the Ki67 proliferation index to the PSOGI PMP classification provided two different subcategories of the extensive HG-PMP group (HG-PMP ≤15% and HG-PMP >15%) with different survival in a previous unicentric study. This study aims to carry out an external and multicentre validation of this new proposed classification.
Method: It was a prospective analysis of samples from a historical and international cohort of patients. A representative area with higher cellular density was used to determine the Ki67%. The Ki67 proliferation

* Corresponding author. Unit of Surgical Oncology, Department of Surgery, and Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, Córdoba, 14004, Spain.
** Corresponding author. Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Reina Sofia University Hospital, Córdoba, Spain.
E-mail addresses: alvaroarjona@hotmail.com (A. Arjona-Sanchez), b72rorua@uco.es (A. Romero-Ruiz).
@alarjosan (A. Arjona-Sanchez)
[1] Arjona-Sanchez A. and Martínez-Lopez A. have contributed equally on this study.

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index (%) was determined in all the HG-PMP patients. A Cox proportional hazard models and multivariable COX models were used. The Kaplan–Meier method and the two-tailed log-rank test were used to analyse the effect of different PSOGI-Ki67 categories on OS and DFS. Its predictive accuracy was analysed using Harrel's C-index and the ROC curve. The calibration was performed using the calibration plots matching.

Results: After exclusions, 349 patients were available for analysis. The 5-years OS were 86% for LG-PMP, 59% for HG-PMP≤15, 38% for HG-PMP>15 and 42% for SRC-PMP ($p = 0.0001$). The 5-years DFS were 49% for LG-PMP, 35% for HG-PMP≤15, 16% for HG-PMP>15 and 18% SRC-PMP ($p = 0.0001$). The discrimination capability of PSOGI-Ki67 was validated.

Conclusion: the PSOGI-Ki67 classification discriminates and predicts the OS and DFS in patients with PMP dividing the HG-PMP category into two well-defined sub-categories. The Ki67 proliferation index should be incorporated routinely in the pathology report for these patients.

1. Background

Pseudomyxoma peritonei (PMP) is a rare malignant disease characterised by the progressive and multifocal accumulation of abundant mucinous tumour tissue in the peritoneal cavity. It is generally associated with a perforated epithelial neoplasm of the appendix [1]. The recommended treatment is, whenever possible, cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) in reference centres [2].

In the past, the histological classification and definition of PMP have been somewhat challenging because of the confusing and overlapping terminology used to refer to it. After building and reaching an extensive consensus, in 2016, the Peritoneal Surface Oncology Group International (PSOGI) established a new classification [3]. It divides PMP into three groups and excludes acellular mucinous-type lesions from its definition. These three groups are defined as PMP with low-grade histological characteristics (LG-PMP), PMP with high-grade histology (HG-PMP), and PMP with the presence of signet ring cells (SRC-PMP). Recently, this classification has been validated due to its capacity to predict overall survival (OS) as well as or better than other classifications [4–6].

Since these classifications are only based on histological findings, the molecular profiling of PMP could play an important role in classifying the disease more accurately. Few studies have been published on the molecular features of PMP and their impact on survival [7]. Actually, the presence of *KRAS* mutations, the deficit of mismatch-repair proteins (MMR) and the overexpression of p53 have been studied, but no strong conclusions have been reached regarding the prognosis of the histological aggressivity [7–10].

In this line, Ki67 is a large (395 kDa) nuclear protein present throughout the cell cycle except for the G0 phase, and it is commonly used to assess tumour cell proliferation. The so-named Ki67 proliferation index is a solid prognostic factor for a wide variety of tumours [11,12]. Thus, we performed a preliminary unicentric study [12] that showed that the addition of the Ki67 proliferation index to the PSOGI PMP classification provides two different subcategories of the extensive HG-PMP group (HG-PMP ≤15% and HG-PMP >15%), showing different OS and disease-free survival (DFS). Using these findings, our group proposed a new PSOGI classification combining histology and the Ki67 index [12]. This study aimed to carry out an external and multicentre validation of this new classification using the European COST action EuroPMP network and the Spanish Group of Oncologic Peritoneal Surgery (GECOP).

2. Methods

2.1. Study environment

The present study was included in the PI1901603 study entitled: "Molecular characterization of pseudomyxoma peritonei and the development of biomarkers and target therapies in a human xenograft model" founded by Carlos III Research Institute in 2019. The Regional Ethics Committee code was 5157, with a favourable dictamen for this new issue on 27th October 2021. It was a prospective analysis of the samples from a historical cohort of patients. The data were used to correlate the new PSOGI classification with OS and DFS.

2.1.1. Study population

The present prospective study has evaluated the proposed subcategories of HG-PMP in a multicentre cohort, using a collaborative network established by the COST action 1701 EuroPMP https://europmp.eu, and the Spanish Group of Peritoneal Oncologic Surgery (GECOP). The patients included were treated in reference Units by cytoreductive surgery and HIPEC. All the patients provided informed consent to analyse the tissue samples (following the local protocols).

The sample size of 81 patients in the previous study published by our group identified significant differences. For this multicentre validation, the sample size estimation was n = 86 patients to observe significant differences at 3 years OS rate from 70% (HG-PMP≤15%) to 36% (HG-PMP>15%) (survivals observed in the previous analysis), with a 90% of power and an estimated alpha error of 0,05.

2.1.2. Variables to study

The entire cohort was classified according to the new proposed PSOGI-Ki67 classification into four groups: LG-PMP (Low-grade PMP), HG-PMP-Ki67 ≤ 15% (High-grade PMP), HG-PMP-Ki67 > 15%, or SRC-PMP groups (Signet Ring Cells PMP).

Demographic variables: age (years) and sex (female/male). Histology: PSOGI tumour category, origin and PSOGI-Ki67 tumour category. Operative variables: Peritoneal cancer index (PCI), completeness of cytoreduction (CC score), HIPEC (yes/no). Treatment variables: Neoadjuvant systemic chemotherapy (yes/no), adjuvant systemic chemotherapy (yes/no). Analytic variables: elevated Ca19.9 (>37 U/mL) and elevated CEA (>2.5 ng/mL).

2.1.3. Treatment

The patients included were treated in reference Units by cytoreductive surgery and HIPEC. The volume and extension of the tumour were calculated using the Peritoneal Cancer Index (PCI). The completeness of the cytoreduction score (CC score) was quantified (CC-0 = no residual tumour; CC-1 = residual tumour nodules less than 0.25 cm; CC-2 = residual tumour nodules between 0.25 cm and 2.5 cm; and CC-3 = residual tumour nodules exceeding 2.5 cm). After verifying optimal cytoreduction (CC0–CC1), HIPEC therapy was delivered according to local protocols. All treatments were decided by consensus of a multidisciplinary team.

2.1.4. Specimen characteristics

The samples analysed were from pseudomyxoma peritonei implants of appendiceal origin, collected from historical cohorts of patients. The samples were fixed and embedded in paraffin. Representative tissue blocks with higher cellular density were used for the determination of Ki67%.

2.1.5. Ki67 analysis in HG-PMP patients (Assay methods)

The Ki67 proliferation index (%) was determined in all the HG-PMP patients. The slides were reviewed by a pathologist, and tissue sections were routinely immunostained using an automated slide processing platform on 5 μm sections of the paraffin-embedded blocks. Heat-induced epitope retrieval was performed with BOND Epitope Retrieval Solution 2 for 20 min for all markers. However, this protocol was flexible according to the particular centre's logistics. Although the proposed protocol was the most commonly used, no validated method, according to local protocols in each centre included in the study, could be used. It was preferred that two pathologists evaluate each case and report the mean value of their results. However, this was also flexible according to the possibilities of each centre.

For Ki67, the labelling index was evaluated by calculating the percentage of positively stained cells in 3 different tumour implants when possible, with a count of at least 500 cells in each section. The protocol included the mean Ki67 of these 3 slides as well as the highest positive value found in any of them, so the statistical analysis was performed using both parameters. Positive Ki67 expression was defined as a brownish granular reaction in the nucleus. Staining intensity was not considered relevant. The Ki67 labelling index was calculated as the number of positive cells/counted cells x 100% [12].

2.1.6. Statistical analysis

Continuous data were reported as medians (IQR). Categorical variables were reported as percentages. Data from living patients were censored. A Cox proportional hazard models and multivariable COX models were used to evaluate the association between peri-operative variables and time-to-event outcomes for OS and DFS. The survival curves were calculated using the Kaplan–Meier method and the two-tailed log-rank test to analyse the effect of different PSOGI-Ki67 categories on OS and DFS. OS was calculated from the day of surgery until the death of the patient, regardless of the cause. DFS was calculated from the day of surgery until the diagnosis of a recurrence or death. Statistical significance was considered when the *p*-value was <0.05.

The new classification performance was analysed using Harrel's C-index and the predictive accuracy was evaluated by the integrated area under the ROC curve (AUC). The calibration was performed using the calibration plots matching. To obtain the concordance index (C-index) of OS and DFS we used the '*survival*' package in RStudio (version 4.1.3), using *coxph()* and *Surv()* functions. The method used to evaluate our survival prediction model was the Harrel's C-index, which is independent of the study-specific censoring distribution. Values of the C-index near 1 indicate a high model performance. On the other hand, to perform the calibration plot we used the R packages '*predtools*' and '*magrittr*', employing *glm ()*, *predict.glm ()* and *calibration_plot ()* functions. In both analyses, all the patients were divided in four groups according to the PSOGI classification and the Ki67 (1: Low Grade; 2: High Grade, Ki67 ≤ 15%; 3: High Grade, Ki67 > 15%; 4: Signet Ring Cells). In the calibration plot, the y-axis represents the observed Kaplan-Meier model; the x-axis represents the Cox regression predicted model**.** The remaining analyses were performed using the statistical software SPSS v18 (IBM).

3. Results

The recruitment ended in June 2022, and a total of 568 patients were collected. After exclusions, 363 patients from a total of 16 international reference centres were available for analysis (Fig. 1). The excluded patients were those with any lack of information or

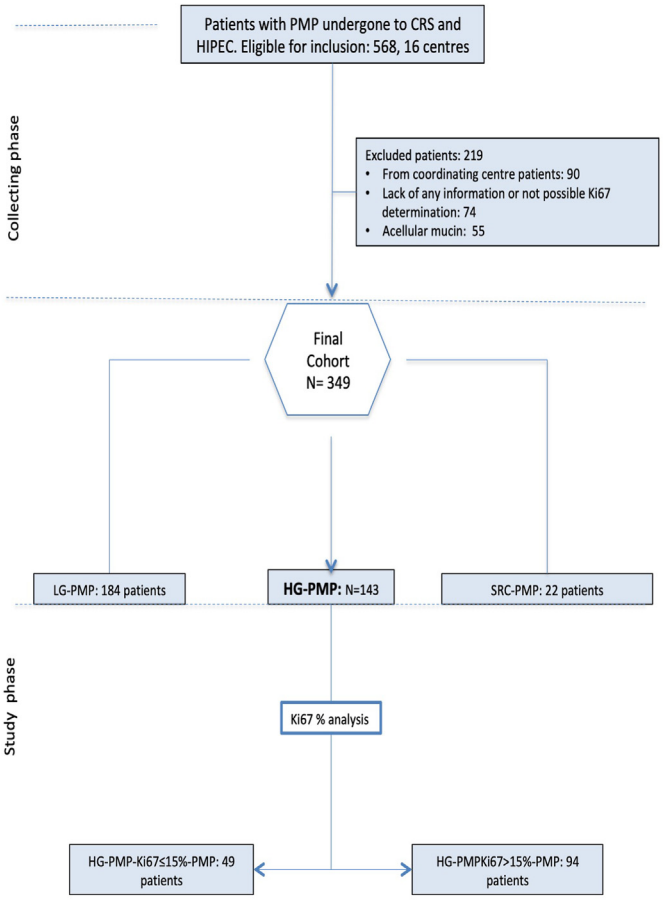


Fig. 1. Flow Chart study.

Table 1
Demographics patient's characteristics. CC score: Completeness of cytoreduction, PCI: peritoneal cancer index, LG: low grade, HG: High grade, SRC: signet ring cell. ^ Calculated out 174 patients. Entire cohort was presented (n = 479) excluding coordinator centre. Cox Regression analysis performed in the selected cohort (349) for overall survival (OS) and disease free survival (DFS), * multivariate analysis, HR: Hazard ratio, CI 95%: Confidence Interval 95%.

Variable	Median (IQR) or Percentage (%)		HR (CI 95%) OS	HR (CI 95%) OS*	HR (CI 95%) DFS	HR (CI 95%) DFS*
Age (years)	59 (42–76)		1.23 (0.6–1.3)		1.45 (0.7–1.2)	
Female	216 (62%)		0.89 (0.8–1.1)		1.67 (0.8–1.3)	
CA 19.9 elevated	181 (52%)		1.66 (0.7–3.7)	2.25 (1.32–3.84)	2.11 (1.1–3.1)	2.17 (1.4–3.2)
Neoadyuvant	33 (19.6%)^		1.44 (0.6–3.1)		1.36 (0.6–2.6)	
CC Score	CC0: 194 (55.5%)					
	CC1: 96 (27.4%)		0.83 (0.3–2.1)	1.35 (0.71–2.58)		
	CC2: 39 (11.1%)		2.63 (0.5–13.1)	6.43 (3.40–12.18)		
	CC3: 20 (5.8%)		4.35 (1.4–13.4)	6.39 (2.86–14.28)		
PCI >21	200 (58%)		1.40 (0.6–3.1)		1.54 (0.8–2.7)	1.53 (1.0–2.2)
PCI	23 (4–39)					
PSOGI Ki67 (n = 363)	LG: 200 (47.2%)					
	HGKi67 ≤ 15: 51 (12%)		2.65 (0.9–7.1)	2.52 (1.32–3.84)	2.26 (1.1–4.5)	1.72 (1.0–2.8)
	HGKi67 > 15: 90 (22.4%)		5.00(1.9–13.2)	5.56 (3.13–9.86)	3.02 (1.4–6.1)	2.83 (1.8–4.4)
	SRC: 22 (5%)		7.11 (0.8–63.3)	4.94 (2.03–11.98)	3.86 (0.8–17.3)	3.70 (2.0–6.6)
	Acellular mucin: 13%		–	–	–	–
Recruitment by centre included in PSOGI-KI67 study.	Dublin, Ireland	104				
	H.U. Gregorio Marañon	87				
	H.U. Fuenlabrada	66				
	Charité Hospital, Berlin	62				
	NPO HIPEC ISTANBUL	40				
	IOV-IRCCS (Padova)	31				
	IRCCS Istituto Nazionale dei Tumori, Milan	26				
	Cancer Institute of Montpellier	16				
	Norwegian Radium Hospital	14				
	Centre Hospitalier Lyon Sud	12				
	Peritoneal Malignancy Institute Basingstoke UK	9				
	Ghent University Hospital, Belgium	7				
	I. C. de l'Ouest Paul Papin, Angers	2				
	CHRU Hautepierre – Strasbourg	2				
	APHP Saint Louis	1				

acellular mucin in the pathology report and the patients from the coordinating centre cohort (used in the internal validation). Patient demographics are shown in Table 1.

3.1. Survival analysis

The Kaplan Meier and log-rank test showed a statistical difference between the different categories of PSOGI-Ki67 classification. Cox regression analysis showed a significant hazard ratio for the different PSOGI-Ki67 categories related to OS and DFS (Fig. 2 and 3). The median follow-up was 31(14–68) months.

The OS Cox multivariable analysis showed as predictive factors: elevated CA19.9, CC score and the PSOGI-Ki67 (Table_1). The median OS was 141 (130–153) months for LG-PMP, 80 (49–111) months for HG-PMP≤15, 29 (21–37) months for HG-PMP>15 and 56 (15–96) months for SRC-PMP. The 5 years overall survival rates were 86% for LG-PMP, 59% for HG-PMP≤15, 38% for HG-PMP>15 and 42% for SRC-PMP (p = 0.0001) (Fig. 2).

The DFS Cox multivariable analysis showed as predictive factors: elevated CA19.9, PCI>21 and PSOGI-Ki67 (Table_1). The median DFS was 53 (38–67) months for LG-PMP, 24 (16–32) months for HG-PMP≤15, 12 (8–15) months for HG-PMP>15 and 10 (0–20) for SRC-PMP. The 5 years DFS rates were 49% for LG-PMP, 35% for HG-PMP≤15, 16% for HG-PMP>15 and 18% for SRC-PMP (p = 0.0001) (Fig. 3).

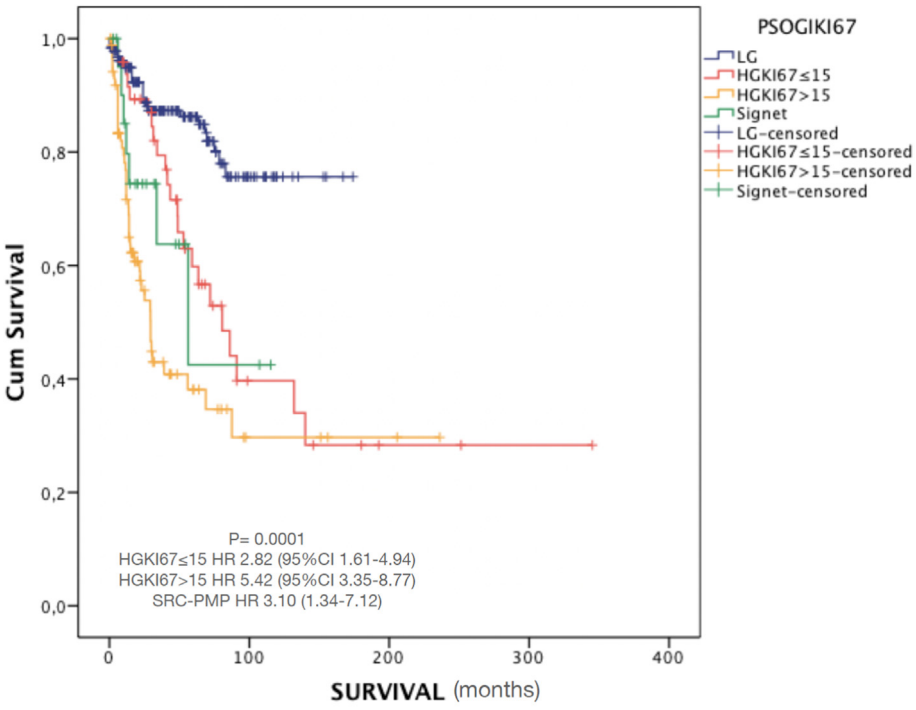
In exploratory survival analysis, there were no differences in OS or DFS when HG-PMP>15 and SRC-PMP were compared, p = 0.39 and p = 0.13, respectively (Suppl.Fig. 1). Additionally, differences in OS and DFS were found between HG-Ki67 ≤ 15 and HG-Ki67 > 15 categories, p < 0.001 (Suppl. Figure 2).

The discrimination capability of PSOGI-Ki67 for OS was validated: the area under the ROC curve was 0.70 (Fig. 4.A), and Harrel's c-index was 0.68. The calibration plots for OS showed a high predictive capability for PSOGI-Ki67 (Fig. 5.A). The discrimination capability of PSOGI-Ki67 for DFS was validated, showing a moderate accuracy: the area under the ROC curve was 0.63 (Fig. 4.B), and the Harrel's c index was 0.65. The calibration plot showed high predictive accuracy for DFS of PSOGI-Ki67 (Fig. 5.B).

4. Discussion

After a preliminary report that divided the HG-PMP category into two well-defined subcategories with different OS and DFS according to the Ki67 proliferation index, we have conducted an external validation for this new proposal PSOGI-Ki67 classification in PMP using a collaborative international network belonging to EuroPMP COST action and the Spanish Group of Peritoneal Oncologic Surgery (GECOP). This multicentre validation provides strong evidence to consider the use of this classification routinely in order to improve the diagnosis and management of PMP.

Given its particular biological and histological characteristics, the nomenclature used to describe PMP has not yet been standardized, but the latest classification from a PSOGI consensus [3], was validated to predict the survival of these patients [4–6]. The PSOGI PMP classification defines the HG-PMP group as including one or more of these features: destructive invasion, high cytologic



Patients at risk. (Censored)	0m	12m	36m	60m
LG	183	154 (20)	102 (40)	69 (31)
HGKi67≤15%	47	44 (1)	31 (6)	19 (5)
HGKi67>15%	87	59 (9)	21 (16	14 (5)
SRC-PMP	21	15(2)	6(7)	2(3)

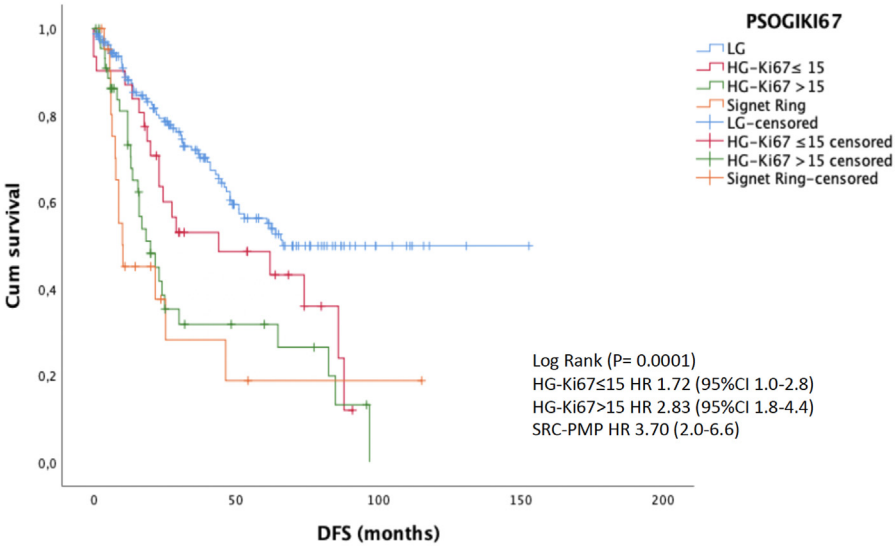
Fig. 2. PSOGI-Ki67 Overall Survival Kaplan Meier curve and log-rank test estimation. HR: Hazard Ratio, CI95%: Confident Interval 95%, LG: Low grade PMP, HG: High grade PMP, SRC: Signet ring cells PMP.

grade, high tumour cellularity, angiolymphatic invasion or perineural invasion [3]. This category includes a large number of patients who might present different outcomes after CRS + HIPEC. This heterogeneity in therapeutic responses warrants a more precise stratification of cases, which remains unmet. On this issue, the characterization of tumour's molecular profile might help to prognosticate patients more accurately [7,13]. In the HG-PMP category, different outcomes were shown when it was divided according to the Ki67 proliferation index (cut-off level of 15%) [12]. Thus, a new sub-categorization into the HG-PMP group was proposed originating a new PSOGI-Ki67 classification.

External validation is required to determine the reproducibility and generalizability of a prediction classification to new and different patients [14]. External validation mainly provides evidence on the generalizability to different patient populations. According to this principle, we have used an international and multicentre cohort of patients using the EuroPMP network COST action in order to provide a large cohort of patients with differences in geographical origins, pathology protocols or surgical management. Although the analysis was performed using a historical cohort, the Ki67 determination was performed prospectively in all the centres involved, which implied an important and collaborative effort.

The Ki67 cut-off of 15% was established in the preliminary study [12] where its predictive value for OS and DFS was statistically significant to discriminate the two sub-categories in HG-PMP proposed. The analysis of Ki67 index has been performed in each centre and ideally, was designed for two pathologists's examinations using the three most representative slides for each patient. One of the limitations of PMP is the paucity of tumour cells, implying the need for pathologist expertise in assessing the Ki67 index. All the groups involved in this study are reference units in the management of PMP.

The Ki67 labelling index has been included as an important prognostic factor and decision-making feature for several cancers. This is the case for the gastrointestinal and pancreatic neuroendocrine tumour classifications, which are based on the Ki67 labelling index [15]. Other tumours, such as breast, prostate or renal cancer, also use this index to establish the prognosis and help in decision-making for the treatment and surveillance of these patients [16]. Recently, one study in diffuse malignant peritoneal mesothelioma has established a cut-off of 9% for the Ki67 index, which implies an important effect on the prognosis of these patients [11]. To incorporate the Ki67 index to the PMP workup including, not only histological features but also molecular biomarkers in the classification, is a step forward to improve the management of these patients. In this study, the new PSOGI-Ki67 classification has shown important differences in OS and DFS



Patients at risk. (Censored)	0m	12m	36m	60m
LG	163	152 (7)	128 (12)	104 (11)
HGKi67≤15%	30	19 (1)	12 (3)	9 (2)
HGKi67>15%	45	34 (5)	8 (7)	6 (2)
SRC-PMP	21	8(2)	3(2)	1(0)

Fig. 3. PSOGI-Ki67 Disease Free Survival Kaplan Meier curve and log-rank test estimation. HR: Hazard Ratio, CI95%: Confident Interval 95%, LG: Low grade PMP, HG: High grade PMP, SRC: Signet ring cells PMP. PSOGI-KI67 Kaplan Meier DFS curve.

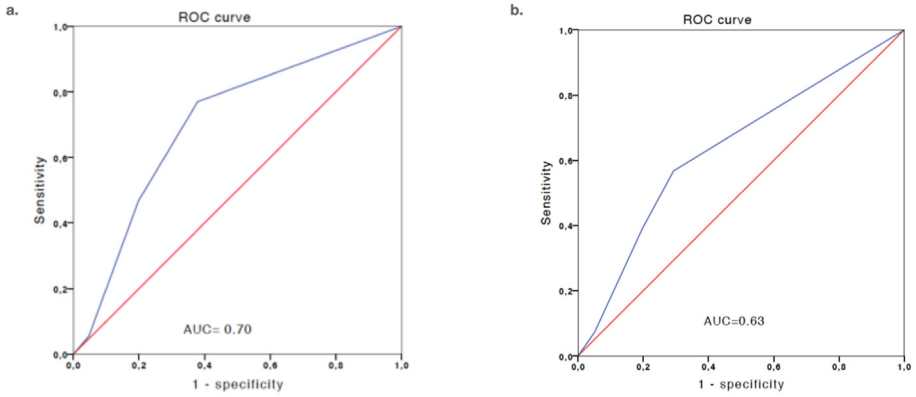


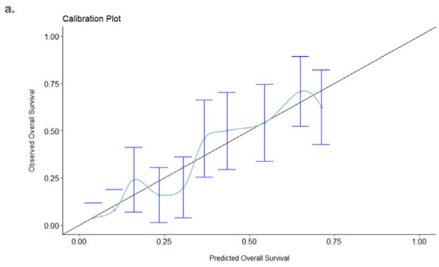
Fig. 4. ROC curve for PSOGI-Ki67 predictive accuracy for **A**.- OS and **B**.- DFS. AUC: Area Under Curve.

according to an increased risk of death or recurrence for each subcategory. Calibration and discrimination analysis showed a good prediction capability for OS and moderate/good prediction capability for DFS.

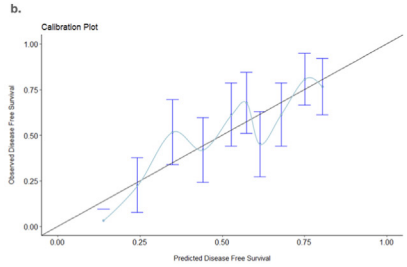
The exploratory analysis showed similar survival outcomes between HG-PMP>15 and SRC-PMP patients, being two different histologic categories. This finding supports the conclusion that patients classified in the HG-PMP>15 and SRC-PMP categories must be carefully included for CRS-HIPEC or considered for neo or adjuvant systemic chemotherapy [17].

Our study has some limitations owing to heterogeneity and eye-based Ki67 determination, which is routine in daily clinical practice. We tried to solve this limitation by using two different pathologists providing a consensus in each case. However, the final objective of external validation is to test it in the most real conditions (different centres, pathologists, reactions and protocols) as possible. In this sense, we have demonstrated an external validation of PSOGI-Ki67 classification, and it might be used in daily clinical practice without being limited by aspects of pathological criteria or tissue processing protocols in different centres.

In conclusion, our study suggests that the PSOGI-Ki67 classification discriminates and predicts the OS and DFS in PMP patients, dividing the HG-PMP category into two well-defined sub-categories. The Ki67 proliferation index should be incorporated routinely in the pathology report for these patients.



	decile	obsRate	obsRate_SE	obsNo	predRate	obsRate_UCL	obsRate_LCL
1	1	0.0000000	0.00000000	25	0.03488584	0.0000000	0.00000000
2	2	0.1200000	0.06633250	25	0.08505318	0.2500117	-0.01001169
3	3	0.2000000	0.08164966	25	0.12839866	0.3600333	0.03996667
4	4	0.0000000	0.00000000	25	0.21047072	0.0000000	0.00000000
5	5	0.4000000	0.10000000	25	0.27676467	0.5960000	0.20400000
6	6	0.4166667	0.10279899	24	0.34370289	0.6181527	0.21518064
7	7	0.4583333	0.10389457	24	0.46943070	0.6619667	0.25469997
8	8	0.5416667	0.10389457	24	0.60510211	0.7453000	0.33803331
9	9	0.6666667	0.09829464	24	0.67905978	0.8593242	0.47400918
10	10	0.7500000	0.09028939	24	0.71981590	0.9269672	0.57303280



	decile	obsRate	obsRate_SE	obsNo	predRate	obsRate_UCL	obsRate_LCL
1	1	0.03225806	0.03225806	31	0.1395249	0.09548387	-0.03096774
2	2	0.22580645	0.07633651	31	0.2419296	0.37542602	0.07618689
3	3	0.51612903	0.09123958	31	0.3491496	0.69495862	0.33729945
4	4	0.41935484	0.09009187	31	0.4411146	0.59593491	0.24277477
5	5	0.61290323	0.08892935	31	0.5271355	0.78720475	0.43860171
6	6	0.67741935	0.08534682	31	0.5737046	0.84469912	0.51013959
7	7	0.45161290	0.09085862	31	0.6149349	0.62969581	0.27353000
8	8	0.61290323	0.08892935	31	0.6797293	0.78720475	0.43860171
9	9	0.80645161	0.07213123	31	0.7507077	0.94782881	0.66507441
10	10	0.76666667	0.07854032	30	0.8048050	0.92060570	0.61272763

Fig. 5. Calibration Plot. The dotted line (black) at 45° indicates perfect calibration, as predicted and observed probabilities are equal. The 10 dots represent tenths of the population divided based on predicted probability. The 10% of patients with the lowest predicted probability are grouped together. Within this group, the average predicted risk and proportion of patients who experience the outcome (observed probability) are computed. This is repeated for subsequent tenths of the patient population. The green line is a smoothed lowess line. For a logistic model, this is computed by plotting each patient individually according to their predicted probability and outcome (0 or 1) and plotting a flexible averaged line based on these points. In this calibration plot, we can see that the classification predicts risk closer to the observed risk; For example, when the predicted risk is 60%, the observed risk is 54% in OS. We can observe an over-prediction more extreme for the high-risk x-axis, while the prediction is more accurate when the risk is lower in both OS and DFS. **A**.- Calibration plot for OS. **B**.- Calibration plot for DFS.

CRediT authorship contribution statement

A. Arjona-Sanchez: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **A. Martinez-López:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft. **M.T. Moreno-Montilla:** Software, Validation, Formal analysis, Investigation. **J. Mulsow:** Data curation, Writing – review & editing, Visualization. **P. Lozano-Lominchar:** Data curation, Writing – review & editing, Visualization. **B. Martínez-Torres:** Data curation, Writing – review & editing, Visualization. **B. Rau:** Data curation, Writing – review & editing, Visualization. **E. Canbay:** Data curation, Writing – review & editing, Visualization. **A. Sommariva:** Data curation, Writing – review & editing, Visualization. **M. Milione:** Data curation, Writing – review & editing, Visualization. **M. Deraco:** Data curation, Writing – review & editing, Visualization. **O. Sgarbura:** Data curation, Writing – review & editing, Visualization. **A. Torgunrud:** Data curation, Writing – review & editing, Visualization. **V. Kapenekian:** Data curation, Writing – review & editing, Visualization. **N.J. Carr:** Data curation, Writing – review & editing, Visualization. **A. Hoorens:** Data curation, Writing – review & editing, Visualization. **J.B. Delhorme:** Data curation, Writing – review & editing, Visualization. **R. Wernert:** Data curation, Writing – review & editing, Visualization. **D. Goere:** Data curation, Writing – review & editing, Visualization. **L. Martin-Roman:** Data curation, Writing – review & editing, Visualization. **S. Cosyns:** Data curation, Writing – review & editing, Visualization. **K. Flatmark:** Methodology, Data curation, Writing – review & editing, Visualization. **B. Davidson:** Formal analysis, Data curation, Writing – review & editing, Visualization. **L. Khellaf:** Data curation, Writing – review & editing, Visualization. **F. Pereira-Perez:** Data curation, Writing – review & editing, Visualization. **L. Rodriguez-Ortiz:** Data curation, Writing – review & editing, Visualization. **A. Ibáñez-Costa:** Data curation, Writing – review & editing, Visualization. **A. Romero-Ruiz:** Data curation, Writing – review & editing, Visualization, All the authors have been involved in the research design, revising the paper and approving the submitted version. Additionally, AAS and AML drafted the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.03.206.

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