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ORIGINAL ARTICLE

# Comparative Study of Different Classification Models in Renal-Cell Carcinoma

Alejandro José Sastre-Heres[1,2] · Irene Iglesias[2] · Miguel Alaguero-Calero[3] · Daniel Ruiz-Sánchez[3] · Benito García-Díaz[4] · Jaime Peña-Díaz[5]

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**Abstract**
The aim of this study was to compare the Memorial Sloan-Kettering Cancer Center (MSKCC) and the Cleveland Clinic Foundation (CCF) models of classification of aRCC patients. In addition, the model developed from the pivotal trial of temsirolimus and those proposed by Motzer et al. in 2004, Escudier et al., Heng et al., Choueiri et al. and Bamias et al. were examined. An observational, retrospective study of patients starting first-line systemic therapy was conducted between 2008 and 2011. The variables used to evaluate the classification models were median overall survival (mOS) and median progression-free survival (mPFS). The comparison of different classification models was performed by comparing the area under the ROC (Receiver Operating Characteristic) curve (AUC) for time-dependent variables proposed by Heagerty. Eighty-eight patients were included. When the different models were compared, it was found that although based on the mOS, the Escudier model had better short-term (1-year) prognostic value, followed by the Heng model; in the long term, the models that presented a higher prognosis capacity were the Hudes and CCF models, closely followed by the Heng model. In addition, the Heng model had a slightly higher predictive ability than the other models. Based on the results, and in line with the European society for medical oncology (ESMO) guidelines, it appears that the model of Heng could be the best model to classify patients with aRCC and combines good short- and long-term prognostics while possessing better predictive ability and a more equal distribution of patients.

**Keywords** Renal cell cancer · Classification · Predictive · Prognostic

## Introduction

Renal cell carcinoma (RCC) represents 2–3% of all tumours, and there is a higher incidence in men than in women, with a sex ratio of 2:1 in patients aged between 60 and 70 years [1]. In 2008, the incidence of this cancer was 3.2% in Europe and 2.6% in the United States, with a mortality of 2.6% and 2.9%, respectively. The present study was conducted at the Central University Hospital of Asturias (HUCA), the referral hospital for the treatment of RCC in the Principality of Asturias, Spain. In 2009, the population of Asturias was 1,085,289 inhabitants in 2009, the incidence of kidney cancer was 2.4 and 2.5% of all cancer deaths that year were due to kidney cancer [2, 3].

RCC has a wide variety of prognostic factors. These can be classified as anatomical, histological, molecular and clinical [1]. Currently, clinical prognostic factors for the classification of patients with advanced RCC (aRCC) [4, 5] are used.

The classification model used in most clinical trials is that published in the Memorial Sloan-Kettering Cancer Center (MSKCC) by Motzer in 2002 [6]. In this model, the following were established as poor prognostic factors: low Karnofsky index (IK <80%), lactate dehydrogenase levels greater than 1.5 times the upper limit of normal (LDH >1.5 ULN), haemoglobin levels below the normal limit (Hb < LLN),

✉ Alejandro José Sastre-Heres
asastre@ohsjd.es

1 Servicio de Farmacia, Hospital San Juan de Dios de Zaragoza, C/ Paseo Colón n°14, 50006 Zaragoza, Spain

2 Faculy of Pharmacy, University Complutense of Madrid, Ciudad Universitaria, Plaza Ramon y Cajal, 28040 Madrid, Spain

3 Hospital Pharmacy Department, Hospital Universitario Central de Asturias, C/ Julián Clavería s/n, 33006 Oviedo, Asturias, Spain

4 Hospital Universitario Severo Ochoa, C/ Avenida de Orellana, s/n, 28911 Leganés, Madrid, Spain

5 Faculty of Pharmacy, (Spanish Society of Hospital Pharmacy)-University of Granada, Campus Universitario de Cartuja, 18071 Granada, Spain

corrected calcium levels above 10 mg/dL (CC >10 mg/dL) and time between diagnosis and the start of systemic therapy of less than 1 year (TDT <1 year). In this model, patients are stratified into three groups of risk or prognosis, depending on the number of risk factors.

Since the publication of this classification, new prognostic factors related to patient survival and new ways of classifying patients according to these have appeared. In 2004, Motzer et al. [7] simplified the previous classification model to reduce the number of poor prognostic factors when classifying patients: IK <80%, CC >10 mg/dL, and Hb < LLN. In 2005, Mekhail at the Cleveland Clinic Foundation (CCF) [8] conducted a study validating the factors in the MSKCC and adding the previous administration of radiotherapy and the presence of individual metastases in the retroperitoneal lymph, lung and liver. In the same study, it was found that the latter factor – the location of individual metastases – could be replaced by the number of metastatic sites, with the presence of two or more metastatic sites being a negative prognostic factor. From previous tests, Hudes et al. [9], in the pivotal trial of temsirolimus, established a group with poor prognosis, which would indicate the suitability of the drug from factors of the MSKCC model and added the presence of two or more sites of metastases from the Mekhail study as a factor [8].

In 2007, Escudier [10] identified five factors of poor prognosis in a multivariate analysis: two or more metastatic sites, time from nephrectomy to metastatic disease of less than 2 years, alkaline phosphatase >ULN, abnormal corrected calcium levels and LDH >1.5 ULN. Finally, patients were stratified into four groups of risk or prognosis based on these factors. In the same year, Choueiri [11] presented a series of clinical factors to predict survival: TDT <2 years; baseline platelet count >300 K/μL, baseline neutrophils >4.5 K/μL; CC <8.5 mg/dL or >10 mg/dL. In a study published in 2009 by Heng et al. [12], four of the five prognostic factors established by the MSKCC (Hb, CC, TDT, IK) were validated [6], and platelet levels and neutrophils above the upper limit of normal were also found to be prognostic factors. That same year, Bamias et al. [13] proposed a simplified model stratifying patients into two groups in which the following were identified as negative prognostic factors: TDT ≤1 year, number of metastatic sites and ECOG (Eastern Cooperative Oncology Group) performance status ≤1. The different classification models are summarised in Table 1.

In clinical practice and in most clinical trials, the most commonly used model is that proposed by Motzer at the MSKCC [6]. However, the use of the Heng model is increasing [12], and it is the one that appears in the European Society for Medical Oncology (ESMO) [4] guidelines as the validated and update of the Motzer model at the MSKCC.

The identification and validation of both prognostic and predictive factors and the classification models based on these factors may contribute not only to the selection of patients in

**Table 1** Summary of the different classification models under study

| Classification model | MSKCC | Mekhail | Hudes | Motzer 2004 | Escudier 2007 | Choueiri | Heng | Bamias |
|---|---|---|---|---|---|---|---|---|
| Risk factors | KI <80%<br>LDH >1.5 ULN<br>Hb < LLN<br>CC<br>>10 mg/dL<br>TDT<br><1 year | KI <80%<br>LDH >1.5ULN<br>Hb < LLN<br>CC >10 mg/dL<br>TDT <1 year<br>≥2 Mx sites (lung, liver and retroperitoneal lymph)<br>Previous Radiotherapy | KI <80%<br>LDH >1.5 ULN<br>CC >10 mg/dL<br>Hb < LLN<br>TDT <1 year<br>≥2Mtx sites (anyplace) | KI <80%<br>Hb < LLN<br>CC<br>>10 mg/dL | TNefMx <2 years<br>ALP > ULN<br>CC >10 mg/dL or <8.5 mg/dL<br>LDH >1.5 ULN<br>≥2Mtx sites (lung, liver, bone or retroperitoneal lymph) | TDT <2 years<br>PLAT >300 k/meL<br>NEUT >4.5 k/meL<br>CC >10 mg/dL or <8.5 mg/dL | IK <80%<br>Hb < LLN<br>CC<br>>10 mg/dL<br>TDT<br><1 year<br>PLAT<br>>LSN<br>NEUT<br>>LSN | TDT ≤1 year<br>ECOG >1<br>≥2Mtx sites (lung, liver, nodes, bone, brain, renal bed) |
| Risk groups | GP: 0 RF<br>IP: 1–2 RF<br>PP: >2 RF | GP: ≤1 RF<br>IP: 2 RF<br>PP: >2 RF | GP: ≤1 RF<br>IP: 2 RF<br>PP: >2 RF | GP: 0 RF<br>IP: 1 RF<br>PP: >1 RF | GP: 0 RF<br>IP-1; 1 RF<br>IP: 2 RF<br>PP: >2 RF | GP: ≤1 RF<br>IP: 2 RF<br>PP: >2 RF | GP: 0 RF<br>IP: 1–2 RF<br>PP: >2 RF | GP: ≤1 RF<br>PP: >1 RF |

CC, corrected serum calcium; ECOG, Eastern Cooperative Oncology Group performance; FA, alkaline phosphatase; GP, good prognosis group; Hb, hemoglobin; IK, Karnofsky index; IP, intermediate prognosis group; LDH, lactate dehydrogenase; LLN, lower limit normal; Mtx, metastasis; NEUT, neutrophil count; PG, prognostic group; PLAT, platelet count; PP, poor prognosis group; RF, risk factor count; TDT, time from diagnosis to treatment; TNefMx, time from nephrectomy to metastasis; ULN, upper limit normal

**Table 2** Results of different classification models

| Classification model | PG | % Patients | | AUC | | |
|---|---|---|---|---|---|---|
| | | Published | Our study | | Published | Our study |
| MSKCC | GP | 18% | 26% | OS | 0.661 | 0.640 |
| | IP | 62% | 42% | | | |
| | PP | 20% | 32% | PFS | 0.52–0.65 | 0.611 |
| CCF | GP | 37% | 44% | OS | NA | 0.674 |
| | IP | 35% | 20% | | | |
| | PP | 28% | 36% | PFS | NA | 0.606 |
| Hudes | GP | NA | 35% | OS | NA | 0.656 |
| | IP | | 17% | | | |
| | PP | | 48% | PFS | NA | 0.604 |
| Motzer 2004 | GP | 42% | 36% | OS | NA | 0.646 |
| | IP | 35% | 25% | | | |
| | PP | 23% | 39% | PFS | NA | 0.617 |
| Escudier | GP | 37% | 7% | OS | NA | 0.650 |
| | IP-1 | 46% | 41% | | | |
| | IP-2 | 14% | 28% | PFS | NA | 0.618 |
| | PP | 3% | 25% | | | |
| Choueiri | GP | 53% | 31% | OS | NA | 0.608 |
| | IP | 23% | 37% | | | |
| | PP | 25% | 31% | PFS | NA | 0.582 |
| Heng | GP | 23% | 27% | OS | 0.73[1] | 0.653 |
| | IP | 51% | 36% | | | |
| | PP | 26% | 37% | PFS | NA | 0.627 |
| Bamias | GP | 65% | 55% | OS | 0.672 | 0.629 |
| | PP | 43% | 45% | PFS | NA | 0.601 |

AUC, area under the ROC curve; PFS, progression-free survival; OS, overall survival; GP, good prognosis group; IP, intermediate prognosis group; PG, prognostic group; PP, poor prognosis group; NA, not available; [1] : C index

clinical trials but also to the identification of groups of patients who may benefit the most from a particular treatment. It can also provide better information to patients about their prognosis. However, the validity of different prognostic and predictive factors evaluated vary from one study to another and from one evaluated treatment to another [14]. These differences may be due to the different methodologies, as well as to the types and characteristics of the population studied in various tests, and the best classification model is still undecided [4].

The effectiveness of first-line treatment in RCCa in some patients included in this study (65 patients, included between January 2008 and November 2010), classified by the poor prognostic factors established by MSKCC plus one validated by Mekhail et al. (two or more metastatic sites, only when considering pulmonary, retroperitoneal lymph node and hepatic metastatic sites), was reported in Molecular and Clinical Oncology, November 2014.

The main objective of this study was to compare the classifying models of patients proposed by the MSKCC [6] and Mekhail [8] and the model developed from the pivotal trial of temsirolimus by Hudes et al. [9], as well as the models proposed by Motzer et al. in 2004 [7], Escudier et al. [10], Choueiri et al. [11], Heng et al. [12] and Bamias et al. [13] (Table 1).

## Methods

An observational, retrospective study was undertaken in patients initiating first-line systemic treatment for aRCC in HUCA between January 1, 2008 and December 31, 2011. Patients were monitored until July 2013. Patients who developed other advanced malignancies requiring chemotherapy were excluded as were those who showed a predominance of sarcomatoid component histology.

The variables used for evaluating classification models were median overall survival (mOS), followed by median progression-free survival (mPFS). The mOS was calculated from the date of the start of treatment until the date of death from any cause or, failing that, until the beginning date of palliative treatment. The mPFS was calculated as the time from the date of the start of treatment to the date of disease progression or death. Both were determined by the Kaplan–Meier method, and the potential differences between first-line treatment and groups with different prognoses were analysed by using the log-rank test. These differences were considered statistically significant if they were associated with a value of $p < 0.05$.

The comparison of the different classification models set out in the Objectives paragraph was made by comparing the

**Table 3** mPFS of first-line therapy and mOS, separated according to prognostic classification group

| Classification Model | Risk Group | mOS (months.IC95) | mOS Significance | mPFS (months.IC95) | mPFS Significance |
|---|---|---|---|---|---|
| MSKCC | GP | 34.4 (22.7–46.1) | $p = 0.000$* | 10.4 (8.1–12.8) | $p = 0.003$* |
| | IP | 13.2 (12.4–14.1) | | 6.0 (5.2–6.9) | |
| | PP | 6.3 (1.7–11.0) | | 3.4 (1.2–5.6) | |
| CCF | GP | 36.4 (27.7–41.1) | $p = 0.000$* | 12.5 (8.9–16.1) | $p = 0.009$* |
| | IP | 13.2 (10.9–15.5) | | 5.6 (4.2–7.1) | |
| | PP | 6.5 (3.8–9.1) | | 3.8 (1.8–5.7) | |
| Hudes | GP | 36.4 | $p = 0.000$* | 10.4 (6.7–14.1) | $p = 0.004$* |
| | IP | 13.2 | | 5.9 (5.6–6.3) | |
| | PP | 8.4 | | 3.8 (2.5–5.0) | |
| Motzer 2004 | GP | 34.4 (26.9–41.9) | $p = 0.000$* | 10.4 (5.4–15.5) | $p = 0.002$* |
| | IP | 13.2 (10.6–15.8) | | 5.9 (5.5–6.3) | |
| | PP | 8.4 (3.9–12.9) | | 3.5 (1.3–5.7) | |
| Escudier | GP | NA | | 9.2 (0.0–23.5) | |
| | IP-1 | 33.3 (26.9–39.7) | | 10.1 (7.2–13.0) | |
| | IP-2 | 18.4 (7.8–29.0) | | 6.3 (2.7–10.0) | |
| | MP | 6.3 (2.6–10.0) | | 3.4 (1.7–5.1) | |
| Choueiri | GP | 34.4 (3.7–65.0) | $p = 0.002$* | 9.2 (4.3–14.1) | $p = 0.083$ |
| | IP | 19.4 (9.4–29.4) | | 6.3 (5.4–7.3) | |
| | PP | 8.4 (4.8–11.9) | | 3.9 (1.3–6.6) | |
| Heng | GP | 34.4 (22.7–46.1) | $p = 0.000$* | 10.4 (8.1–12.8) | $p = 0.001$* |
| | IP | 13.5 (1.4–25.5) | | 6.5 (5.5–7.4) | |
| | PP | 6.3 (0.9–11.8) | | 2.8 (1.0–4.6) | |
| Bamias | GP | 30.6 (25.2–36.0) | $p = 0.000$* | 9.1 (5.8–12.4) | $p = 0.000$* |
| | PP | 8.4 (4.8–11.9) | | 3.7 (2.7–4.7) | |

GP, good prognosis group; IP, intermediate prognosis group; PP, poor prognosis group; CI, confidence interval; mPFS, median progression-free survival; mOS, median overall survival *Differences between groups were considered statistically significant if they were associated with a value of $p < 0.05$

area under the ROC (Receiver Operating Characteristic) curve for time-dependent variables from the model proposed by Heagerty [15]. This ROC curve is commonly used to compare predictive accuracy of different survival models, and this new version proposed by Heagerty is especially useful when the outcome is a censored survival time.

## Results

During the inclusion period, 94 patients initiated first-line systemic treatment for aRCC in HUCA. Of these, five were excluded following the criteria described above in the methodology. Of the 88 patients included in the study, 71 were treated with sunitinib as the first-line treatment and 17 with temsirolimus. Apart from sunitinib and temsirolimus, in successive lines, the treatments used were axitinib, bevacizumab, everolimus, dovitinib, sorafenib and pazopanib.

The median age was 66 years (range: 45–86 years), and 67 patients (76.1%) were men. Median IK at baseline was 77.8% (range: 50–100%). Of all patients, 74 (84.1%) had distant metastases at the time of diagnosis, and 69 (78.4%) had undergone nephrectomy. From a histological point of view, 61 patients (69.3%) had clear cell histology (ccRCC), 8 (9.1%) papillary, 9 (10.2%) mixed, and 1 (1.1%) chromophobe; in the remainder (9.1%), histology could not be obtained.

At the end of the follow-up, 68 patients (77.3%) had died, 4 (4.5%) were receiving palliative care, 12 (13.6%) continued treatment with antineoplastics and 4 (4.5%) remained under observation.

Table 2 shows the distribution of patients in our study according to the different classification models and the respective average AUC (area under the curve) of different classification models compared to the respective published studies based on the mOS and mPFS. Table 3 shows mPFS of first-line therapy and mOS, separated according to prognostic classification group.

## Discussion

If we compare the characteristics of patients included in our study with those observed in the literature [1], we note a similar average age (65.5 vs. 60–70 years) and predominance (76.1%) of males (2: 1). The most frequent histology was clear cell histology (69.3%), followed by papillary (9.1%) and chromophobe (1.1%) histologies. The proportion of histology was lower than that reported in the literature (75–90%, 10–15%

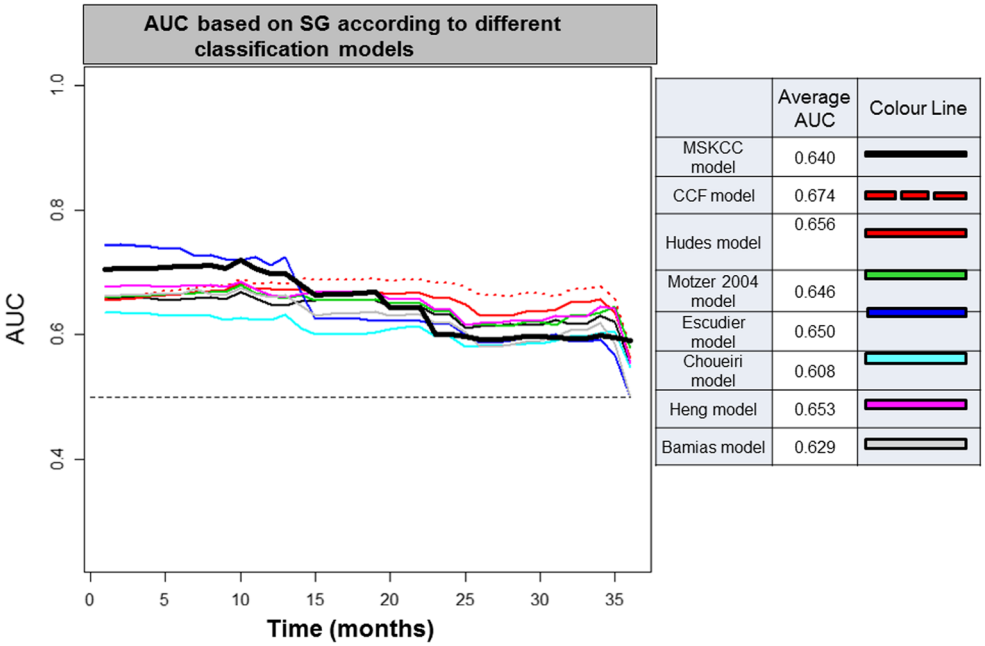


**Fig. 1** AUC base on SG according to different classification models

and 4–5%, respectively) [1, 5, 16, 17], especially in the case of chromophobe histology. This is perhaps a result of the large proportion of mixed histology without a predominant histology (10.2%) or of the proportion of patients for whom data could not be provided from pathologic anatomy (10.2%).

The published results for the respective values differ slightly from those of mPFS and mOS according to each prognostic classification group (Table 3), but this difference could be due to different population characteristics (general state of the patients, proportion in different risk groups, previous treatments, difference in risk factors in the population etc.).

Figures 1 and 2 show the representation of AUC based on the predictive and prognostic ability of patients in our study who were classified according to the different classification models described above. When comparing the different models, we note that, based on the OS, the Escudier model has a better prognostic ability in the short term (1 year) than the other models, as their AUC is closer to 1 in the short term. However, in the long term, the models with the greatest predictive ability are the Hudes and CCF models, followed closely by the Heng model as their AUC is closer to 1 in the long term. Also, the Heng model has a slightly higher predictive

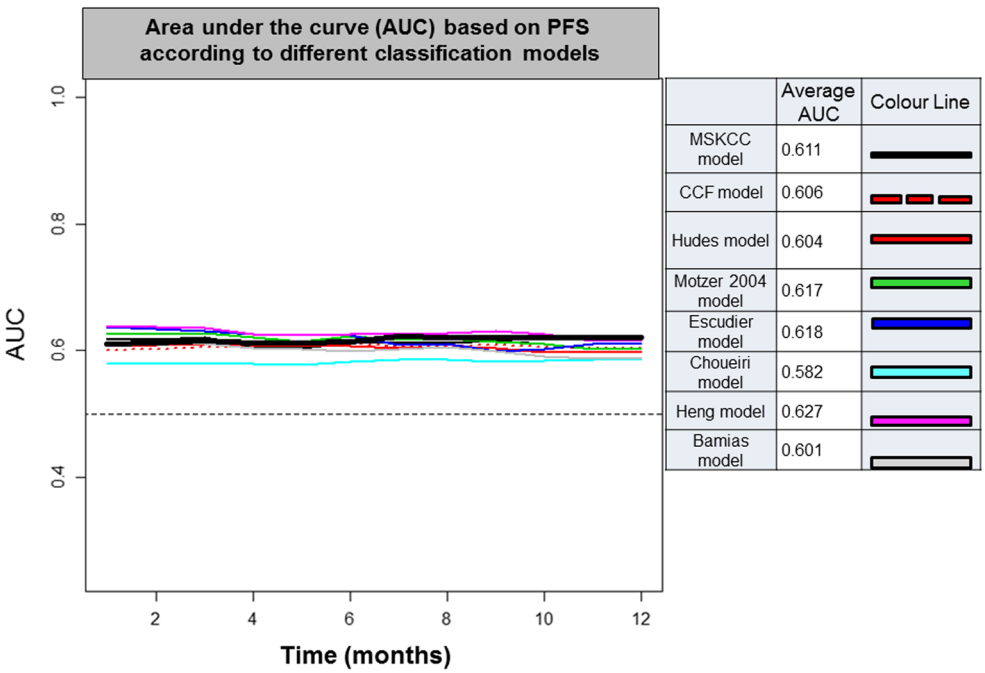


**Fig. 2.** Area under the curve (AUC) based on PFS according to different classification models

ability than the other models, based on PFS, in both the short and long terms, despite their similarly low predictive ability. Regarding the distribution of the patients in the different groups, the Choueiri model, followed by that of Heng, are those with a more homogeneous distribution.

As we can observe in Table 2, the average AUC values obtained are lower than those published regarding mOS in the MSKCC [6] and Bamias [13] models, but within the range with regards to the predictive ability of the mPFS MSKCC model [18]. In addition to the AUC, a similar method of comparing different classification models is the C index, and this value is slightly higher in the published studies of the Heng model [12, 19] compared with the AUC of our study. The differences between published values and those in our study may be due to several factors. In addition to the inherent limitations of observational studies, the main weakness of this study is the small number of deaths included in the study (68, 77.3%), the limited sample size of our study, and the difference between the treatments used in our population and some of the published studies.

## Conclusion

In conclusion, despite the above limitations, this study allows the different classification models to be compared for the first time with a unique methodology and avoiding divergences due to the type and characteristics of the population as well as the treatments used. It reveals not only the prognostic ability of major classification models but also their predictive ability in the era of targeted therapy. Comparing the different classification models based on the results obtained, and in line with the ESMO guidelines, it seems that the Heng model could be the best model to classify patients with aRCC, combining good short- and long-term prognostics. Also, the Heng model appears to have the best predictive ability, though discreet on all models, and to present a more homogeneous distribution of patients among the different groups than most of the other models.

### Compliance with Ethical Standards

**Conflict of Interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Ethical Approval** The Ethics Committee of Central University Hospital of Asturias (Spain) approved the study.

**Informed Consent** Consent was obtained for the use of patient data.

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