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Continuous - Time Markov Modeling of Durvalumab Dynamics after Chemoradiotherapy in Stage III NSCLC (PACIFIC Era): Development, Validation, and Extrapolation

Zurita AJW, Ruíz MAG, Carmona DM, Ibáñez JP, Rivera GC and Sánchez CM*

Department of Radiation Oncology, Hospital Universitario Virgen Macarena, Seville, Spain

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Correspondence:
A.J. Wals Zurita, Department of Radiation Oncology, Hospital Universitario Virgen Macarena, Seville, Spain, Tel: +34660374321; E-mail: amadeo.wals@gmail.com

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Abstract

Background: Immunotherapy in un-resectable stage III NSCLC shows delayed treatment effects and time-varying hazards that challenge proportional-hazards assumptions. We developed a Continuous-Time Markov Chain (CTMC) model - with piecewise hazards - to capture the temporal dynamics of durvalumab after chemoradiotherapy (PACIFIC era), enabling transparent extrapolation beyond early trial landmarks.

Methods: We specified a multi-state CTMC with absorbing death, and clinically interpretable transient states (pre-progression disease control and post-progression). Piecewise transition rates were calibrated to early PACIFIC landmarks (e.g., 0-12-24-36 months) for Overall Survival (OS) and Progression-Free Survival (PFS), using constrained optimization. External validity was assessed by comparing model-implied OS/PFS trajectories against published PACIFIC follow-ups and large real-world evidence. Uncertainty was quantified via parametric resampling of transition intensities and sensitivity to piecewise knots.

Results: The CTMC reproduced the hallmark delayed separation of survival curves and the long-tail behavior typical of immune checkpoint inhibition. When calibrated only to early landmarks, the model generated plausible OS and PFS beyond 36 months, approaching 5-year targets reported in PACIFIC follow-ups (e.g., ~43% OS and ~33% PFS with durvalumab), while acknowledging mild underestimation of late PFS in sensitivity scenarios. Goodness-of-fit remained stable across alternative knot placements; uncertainty widened beyond 60 months, as expected from non-individual data calibration.

Conclusions: A piecewise-hazard CTMC provides a transparent and reproducible framework to model non-proportional, time-dependent immunotherapy effects in stage III NSCLC, reconciling early trial information with clinically coherent long-term projections. This approach can support methodological rigor in survival analysis, scenario planning, and health-economic extrapolation in the PACIFIC setting and similar contexts.

Keywords: Continuous-Time Markov Chain; Non-Proportional Hazards; Immunotherapy; Durvalumab; Pacific; Stage III NSCLC; Survival Extrapolation

Abbreviations

NSCLC: Non-Small-Cell Lung Cancer; cCRT: Concurrent platinum-based Chemoradiotherapy; OS: Overall Survival; PFS: Progression-Free Survival; PACIFIC: Phase III trial of durvalumab after cCRT in unresectable stage III NSCLC; PACIFIC-R: Real-world observational study of durvalumab after Ccrt; PD-L1: Programmed Death-Ligand 1; CTMC: Continuous-Time Markov Chain; Q (generator matrix): Matrix of instantaneous transition rates between states; MSE: Mean Squared Error; CR: Complete Response; PR: Partial Response; SD: Stable Disease; Prog.: Progression; Post-CR relapse: Recurrence after complete response

Introduction

Non-Small-Cell Lung Cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide. Approximately 20%-30% of patients are diagnosed with stage III, locally advanced, unresectable disease [1, 2]. Historically, the standard of care consisted of platinum-based concurrent

Chemoradiotherapy (cCRT), with limited outcomes: median Overall Survival (OS) ranging from 9 to 34 months and 5-year survival rates below 20% [1-3].

The phase III PACIFIC trial (NCT02125461) represented a paradigm shift in this clinical setting. In patients without progression after cCRT, consolidation therapy with durvalumab for up to 12 months significantly improved both Progression-Free Survival (PFS) and OS compared with placebo, with a manageable safety profile and no detrimental effect on quality of life [4-6]. Follow-up analyses confirmed the durability of benefit: at 3 years, the OS rate was 57.0% versus 43.5% with placebo [2], and at 5 years, 42.9% of patients treated with durvalumab remained alive compared with 33.4% in the placebo arm [3].

The efficacy pattern of immunotherapy is characterized by an initial latency reflecting immune activation, followed by prolonged and sustained responses in a subset of patients, sometimes persisting after treatment discontinuation [2-4]. This phenomenon produces survival curves with delayed separation and long tails, reflecting the presence of subpopulations deriving differential benefit.

Real-world evidence has reinforced these findings. In the PACIFIC-R observational study, which included more than 1,100 patients across 10 countries, the 3-year OS rate reached 63.2%, even among subgroups with low PD-L1 expression or treated with sequential chemoradiotherapy [1]. These data consolidate the effectiveness of durvalumab in heterogeneous populations, strengthening its role as the global standard of care for patients with unresectable stage III NSCLC.

Methodological Challenges and Modeling Approach

Immunotherapy poses important methodological challenges, as its temporal dynamics do not conform to the linear assumptions or proportional hazards underlying classical survival models. Recent methodological literature has documented that immunotherapy trials frequently display delayed treatment effects, long-tail survival patterns, and violations of the proportional hazards assumption, which has driven the development of alternative analytical strategies, such as restricted mean survival time and specific models for non-proportional hazards [9-12].

The presence of an initial latency period and prolonged responses in a subset of patients produces survival curves with delayed separation and long tails, which are difficult to capture using standard parametric approaches [2-4]. To address this challenge, it is necessary to explore advanced extrapolation frameworks, such as continuous-time Markov chains, which allow explicit representation of cohort transitions across distinct clinical states (response, stability, progression, recurrence, and death), thereby enabling the derivation of clinically and economically relevant outcomes in a more realistic manner [2, 3, 6].

Materials and Methods

Population and data sources

This analysis is based on the results of the phase III PACIFIC trial (NCT02125461), which enrolled 713 patients with un-resectable stage III NSCLC without disease progression after platinum-based cCRT. In addition to the original publications and their 3- and 5-year updates, real-world evidence was incorporated from the PACIFIC-R observational study, which included 1,154 patients treated across 10 European countries [1]. This dataset was used to externally calibrate and validate the model.

Definition of clinical states

The model was structured into five mutually exclusive clinical states: response (partial or complete after cCRT), stability (without progression or criteria for response), progression, recurrence after complete response (optional in sensitivity analyses), and death (absorbing state). These states reflect the clinical trajectory described in PACIFIC and reproduce both the initial disease dynamics and the patterns of delayed relapse characteristic of immunotherapy [2-4].

Analytical Framework: Continuous-Time Markov Chains

A Continuous-Time Markov Chain (CTMC) model was implemented. Transitions between states were defined by a generator matrix Q, where each element q_{ij} represents the instantaneous rate of change from state *i* to state *j*. Transition probabilities over an interval t were obtained from the matrix exponential:

P(t)=eQt.P(t) = e^{Qt}.P(t)=eQt.

The temporal evolution of the cohort was resolved using the forward Kolmogorov equations, an appropriate framework for processes with nonlinear dynamics such as immunotherapy, and previously applied in economic evaluations and extrapolation models in oncology [7, 8].

Piecewise Calibration

To capture the temporal heterogeneity of immunotherapy, a piecewise calibration strategy was applied:

- 0-12 months
- 12-24 months
- 24-60 months

Within each interval, transition rates were optimized by nonlinear least squares, fitting model-derived Progression-Free Survival (PFS) and Overall Survival (OS) to the observed curves from the PACIFIC trial at follow-up landmarks of 14.5, 33, and 61 months [2-4].

The primary strategy consisted of calibrating the CTMC model piecewise using only landmarks at 0–12-24-36 months, without constraints beyond 48-60 months. This specification reproduces the early survival dynamics and, when extrapolated beyond 36 months, approximates the 5-year landmarks reasonably well, although it does not explicitly capture the immunological heterogeneity underlying long-tail survival.

Sensitivity analyses included:

(i) Recalibration constrained by the OS landmark at 60 months (PACIFIC update);

(ii) Mixture-cure modeling with an “immune control” fraction;

(iii) Flexible hazards using Royston-Parmar spline models.

These alternatives reduced late discrepancies at the cost of increased complexity or anchoring to late data and are therefore reported only as sensitivity scenarios.

External Validation

The calibrated model was contrasted against published 3- and

Table 1: States and transitions with estimated monthly rates (q_{np}, month^{-1}).

Origin state	Destination state	Monthly rate (month^{-1})	Clinical comment
CR	Progression	0.02	Early relapse from CR
CR	Post-CR relapse	0.01	Clinical relapse after complete response
PR	Progression	0.04	Failure after partial response
SD	Progression	0.06	Failure from stable disease
Progression	Death	0.02	Cancer-related mortality in progression
Post-CR relapse	CR	0.02	Re-response (infrequent event)
Post-CR relapse	Progression	0.02	Failure after relapse
Post-CR relapse	Death	0.06	Mortality after relapse

Note: Instantaneous rates estimated from the calibrated generator matrix (see Matrix Q and P(3)). Values may be adjusted by intervals in the piecewise approach; see interval-specific multipliers.

5-year OS and PFS data from PACIFIC [2, 3], as well as real-world estimates from the PACIFIC-R cohort [1]. Model adequacy was assessed both visually (overlay of simulated vs. Kaplan–Meier curves) and quantitatively using the Root Mean Squared Error (RMSE).

Results

States and transitions

The model structure enabled estimation of transition rates among the five predefined clinical states. In the initial interval (0-12 months), transitions from stability to progression predominated, reflecting the high risk of early relapse following cCRT. During the intermediate interval (12-24 months), a progressive decrease in relapse rates and a relative increase in time spent in response were observed. Finally, in the late interval (24-60 months), stabilization occurred with a subset of patients remaining in prolonged response. Although the long tail approximates published data, the model does not explicitly incorporate the biological phenomenon of durable responders (Table1, Figure 1 and 2).

Generator matrix and transition matrices

The calibrated rates were incorporated into the generator matrix (Q), from which transition probabilities at different time horizons were derived. For example, the 3-month transition matrix indicated a cumulative probability of progression of 42% during the first year, consistent with PACIFIC data (44.1%) (Table 2 and 3).

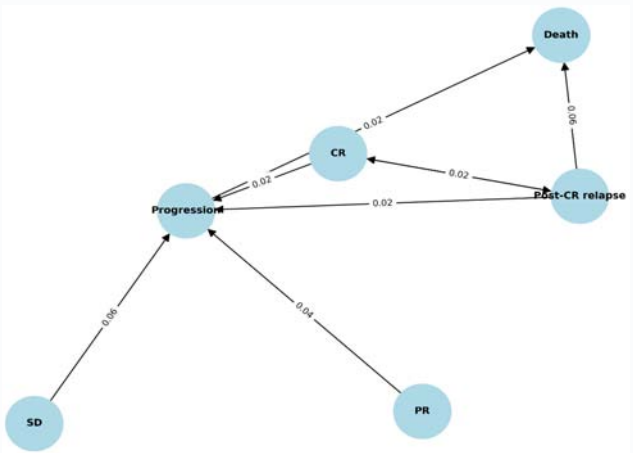

Figure 1: Graph of states and transitions (CTMC model).
Graph of states and allowable transitions for the PACIFIC-era model. Absorbing state is death. Transient states represent disease control before and after progression. Transition intensities are piecewise-constant over predefined intervals.

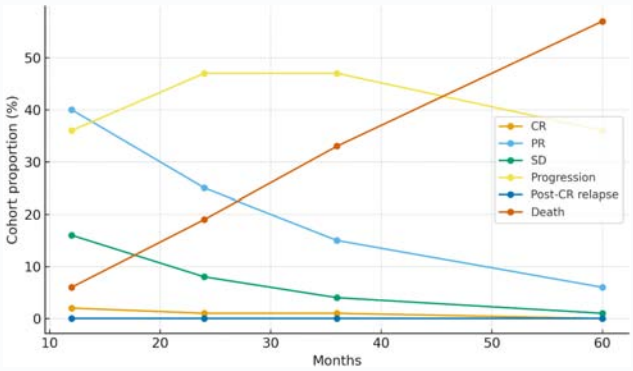

Figure 2: Evolution of the cohort by clinical states.
Stacked area chart of cohort proportions across states under durvalumab after chemoradiotherapy. The model captures early disease-control dominance and the gradual increase of post-progression occupancy, with a persistent long-term non-progressed fraction.

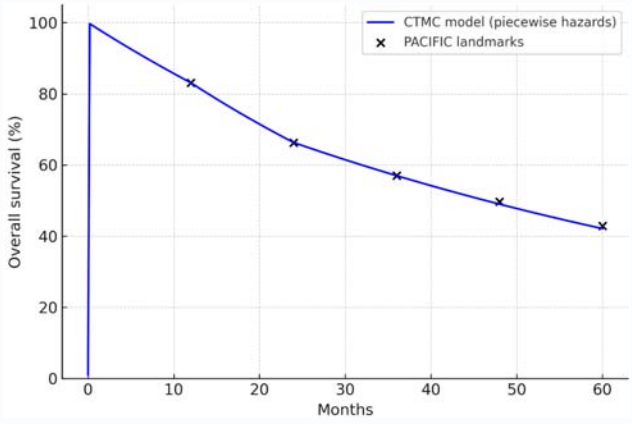

Figure 3: Overall survival (OS).
Overall survival (OS) curve with durvalumab in PACIFIC obtained using a Continuous-Time Markov Chain (CTMC) model with piecewise hazards, calibrated only with early landmarks (0–12–24–36 months) and extrapolated ≥36 months without anchoring to the 60-month survival. Black dots correspond to the published PACIFIC landmarks (12, 24, 36, 48, and 60 months). The model reproduces the initial segment well and reasonably approximates the late landmarks, although it does not explicitly capture the immunological "tail effect.

Cohort distribution at clinical landmarks

The model estimated the distribution of patients across states at clinically relevant time points. At 12 months, most patients were in stability or response; at 24 months, the proportion in progression

Table 2: Generator matrix Q (monthly rates).

	CR	PR	SD	Progression	Post-CR relapse	Death
CR	–0.02	0.00	0.00	0.02	0.01	0.00
PR	0.00	–0.04	0.00	0.04	0.00	0.00
SD	0.00	0.00	–0.06	0.06	0.00	0.00
Progression	0.00	0.00	0.00	–0.02	0.00	0.02
Post-CR relapse	0.02	0.00	0.00	0.02	–0.10	0.06
Death	0.00	0.00	0.00	0.00	0.00	0.00

Note: q_{ij} are instantaneous monthly transition rates (month^{-1}) from state *i* to state *j* ($i \neq j$). The diagonal satisfies $q_{ii} = -\sum_{j \neq i} q_{ij}$.

Table 3: Three-month transition matrix, P(3)=exp(3·Q).

	CR	PR	SD	Progression	Post-CR relapse	Death
CR	0.93	0.00	0.00	0.05	0.02	0.00
PR	0.00	0.88	0.00	0.11	0.00	0.00
SD	0.00	0.00	0.84	0.15	0.00	0.01
Progression	0.00	0.00	0.00	0.93	0.00	0.07
Post-CR relapse	0.05	0.00	0.00	0.06	0.73	0.16
Death	0.00	0.00	0.00	0.00	0.00	1.00

Note: Cumulative 3-month transition probabilities derived from the generator matrix Q.

Table 4: Cohort distribution at time landmarks according to the calibrated CTMC model.

Months	CR	PR	SD	Progression	Post-CR relapse	Death
12	2.0%	40.0%	16.0%	36.0%	0.0%	6.0%
24	1.0%	25.0%	8.0%	47.0%	0.0%	19.0%
36	1.0%	15.0%	4.0%	47.0%	0.0%	33.0%
60	0.0%	6.0%	1.0%	36.0%	0.0%	57.0%

Note: Proportion of the cohort in each clinical state at the indicated months. Derived from the piecewise-calibrated transition matrix.

Table 5: Expected mean time per state (calibrated scenario).

State	Months	Years
CR	0.86	0.07
PR	16.09	1.34
SD	5.57	0.46
Progression	41.21	3.43
Post-CR relapse	0.06	0.01

Note: Calculated with the fundamental matrix $N = (-Q_{TT})^{-1}$; includes transient states (CR, PR, SD, Progression, Post-CR relapse).

increased, but a subgroup remained in sustained response; at 60 months, a stable fraction of patients persisted in prolonged response (Table 4).

Expected time spent in each state

Expected time calculations revealed that patients treated with durvalumab spent, on average, more months in response or stability and fewer in progression compared with placebo. This metric provides a granular view of the clinical benefit, linking the model to quality of life and healthcare resource utilization (Table 5 and 6).

Validation against PACIFIC and PACIFIC-R

Simulated curves (Figures 3 and 4: OS and PFS) demonstrated good agreement with both short- and long-term outcomes. However, concordance in the tail (48-60 months) should be interpreted cautiously, as the model does not explicitly incorporate a state of durable immune control. Piecewise calibration can reproduce late landmarks, but this should not be conflated with a biological representation of long-term responders. Future work may explore mixture-cure or cure-like models to address this limitation.

Discussion

Methodological context: Non-proportional hazards in immunotherapy

The main challenge in evaluating Immune Checkpoint Inhibitors (ICIs) in stage III NSCLC is that their therapeutic effect does not follow a linear dynamic and often violates the proportional hazards assumption of the Cox model. In practice, this results in delayed separation of survival curves and time-varying Hazard Ratios (HRs), as described in methodological analyses of ICI trials. Exclusive reliance on classical tools (Cox with constant HR and standard log-rank tests) may underestimate the true benefit when effects emerge

Table 6: Piecewise multipliers applied to the base Q matrix.

Interval	CR→Prog.	PR→Prog.	SD→Prog.	Prog.→Death	Relapse→CR	Relapse→Prog.	Relapse→Death
0–12 m	0.7×	0.7×	0.8×	0.6×	1.0×	1.0×	0.9×
12–24 m	1.0×	1.0×	1.1×	1.0×	1.0×	1.0×	1.0×
24–60 m	1.2×	1.2×	1.3×	1.3×	0.9×	1.1×	1.2×

Note: Multiplicative factors (Hadamard product) applied by interval to the generator matrix Q to capture temporal heterogeneity.

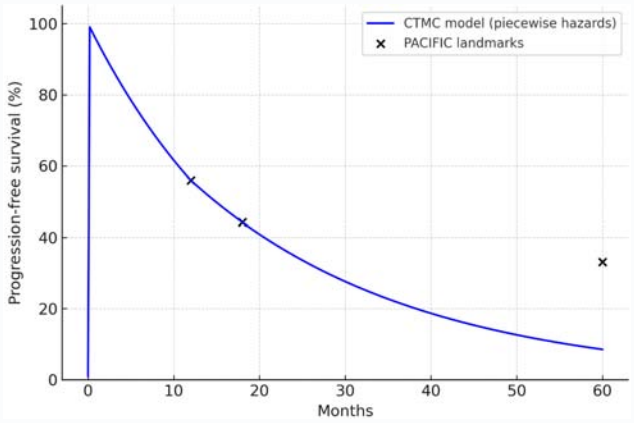

Figure 4: Progression-Free Survival (PFS)
Progression-Free Survival (PFS) curve with durvalumab in PACIFIC, estimated using a Continuous-Time Markov Chain (CTMC) model calibrated only to early landmarks (12 and 18 months; blinded independent central review, NEJM 2017) and extrapolated ≥18 months without anchoring to the 5-year value. The 12- and 18-month landmarks and the approximate 5-year PFS reported in later follow-up are shown as references. The model adequately reflects the initial benefit but underestimates the late progression-free tail.

late [13, 14].

Contribution of the present study: Piecewise CTMC and granular clinical readout

Our Continuous-Time Markov Chain (CTMC) model with piecewise calibration was designed to capture temporal heterogeneity and describe trajectories across clinical states (response, stability, progression, etc.). Compared with purely parametric approaches, interval-based estimation allows distinct transition rates by period, reproduces early landmarks, and provides clinically meaningful metrics (expected time in each state) that can inform medical decision-making and cost-effectiveness assessments. Nonetheless, limitations remain: the model does not yet incorporate an explicit "immune control/cure" state to reflect the long tail, and its primary calibration has been based on the PACIFIC scenario, requiring external validation.

Recommended analytical approaches in the context of non-proportional hazards

We propose complementing CTMC inferences with procedures that are sensitive to time-varying HRs:

• Cox models with time-dependent coefficients to estimate HR(t) and visualize benefit Windows [13, 14].

• Flexible survival models (Royston-Parmar splines on the hazard or log-cumulative hazard scale), which capture smooth changes and enable realistic extrapolations in the presence of long tails [13, 14].

• Weighted log-rank tests (e.g., Fleming-Harrington or late-weighted Rényi), useful when treatment effects emerge after a latency period [13, 14].

Applied in combination, these methods mitigate the risk of type II error when effects are delayed and prevent spurious negative conclusions in global analyses [13, 14].

Role of Bayesian approaches

A gradual implementation of Bayesian analyses is encouraged to incorporate prior evidence and quantify the probability of long-term clinical benefit even when frequentist tests fail to reach global significance. Bayesian inference allows posterior probabilities of HR(t)<1 over temporal windows, which is particularly valuable in ICI settings characterized by prolonged survival tails [13].

Specific relevance in stage III (cCRT+ICI)

In unresectable stage III disease, biological heterogeneity, the interaction with cCRT, and the possibility of salvage therapies condition transition dynamics and interpretation of OS/PFS. Therefore, in addition to the aforementioned methods, it is pertinent to:

• Explore instantaneous and cumulative hazard curves across periods (0-12, 12-24, 24-60 months).

• Evaluate models with a cure fraction or immune-control state to better represent the long tail.

• Integrate data and recommendations from stage III-specific literature to contextualize combined strategies and emerging therapeutic approaches [15].

Limitations and potential sources of bias

The piecewise CTMC is parsimonious and reproduces key landmarks, but its validity depends on: (i) the choice of calibration intervals; (ii) the absence of a "cured" state; (iii) the omission of severe toxicities and salvage therapies from the structure; and (iv) dependence on the dataset used for calibration and extrapolation. These limitations should be addressed through sensitivity analyses (e.g., ±20% variation in interval-specific rates), alternative temporal partitions, and external validation.

Practical implications and future directions

• Dual analytic plan: retain CTMC for clinically interpretable state-time metrics, and add (a) Cox with $\beta(t)$, (b) Royston-Parmar models, and (c) weighted log-rank tests to strengthen inference on HR(t) and long tails [13, 14].

• Bayesian inference: estimate probabilities of sustained benefit by temporal windows and compare decision thresholds (go/no-go) with and without prior evidence [13].

• Model structure: test an extension including an immune-control/cure state and evaluate its impact on OS/PFS and economic outcomes.

• External validation: contrast extrapolations against independent cohorts (e.g., post-marketing registries) and synthesize findings through meta-modeling.

• Stage III focus: align analyses with the biology and clinical logistics of cCRT plus ICI, following state-of-the-art therapeutic pathways [15].

Summary of the discussion

The combination of a piecewise CTMC model - capable of providing granular clinical metrics - with methods explicitly sensitive to non-proportional hazards and Bayesian approaches constitutes a more faithful framework to capture the temporal dynamics of immunotherapy. This integrated strategy reduces the risk of underestimating late effects, enhances clinical interpretability, and strengthens the inferential robustness of results in stage III NSCLC [13-15].

Conclusions

1. The piecewise CTMC model calibrated within 0-36 months parsimoniously reproduces the temporal dynamics of the PACIFIC trial, adequately approximating both Overall Survival (OS) and Progression-Free Survival (PFS) during the early intervals.

2. For OS, long-term extrapolation approximates the 5-year landmarks, although it does not explicitly represent the fraction of patients deriving sustained immunologic benefit.

3. For PFS, the model underestimates long-term survival, underscoring the need to explore hybrid approaches (CTMC with a cure-like component or flexible hazard models) to better capture long tails.

4. The state-based analysis provides clinically and economically meaningful metrics, reflecting not only survival prolongation but also the quality of time spent in each clinical phase.

5. Future research should validate this framework in larger real-world cohorts and compare its performance with alternative extrapolation approaches in immuno-oncology.

Statement on the Use of Artificial Intelligence

Natural language processing-based Artificial Intelligence (AI) tools were employed to support the drafting, organization, and revision of this manuscript. Specifically, ChatGPT (OpenAI, GPT-5 model, 2025) was used as an assistant to structure sections of the text in line with scientific writing conventions in biomedical journals, generate preliminary versions of tables, algorithms, and appendices from the available analytical data, and verify consistency between numerical results, figures, and their description in the text.

AI did not generate original data nor perform statistical or clinical analyses, which were independently executed and validated by the authors. All AI-generated suggestions were critically reviewed, edited, and approved by the investigators before inclusion in the final version of the manuscript. The use of AI was limited to editorial and methodological support tasks, in accordance with international transparency recommendations issued by the ICMJE and COPE.

Conflict of Interest Statement

The authors declare no relevant conflicts of interest for this work. They have not received fees, grants, financial interests, or institutional support from any entities that could have influenced the results or their interpretation.

Ethics Approval and Informed Consent

This manuscript reports a secondary analysis of data previously published in the scientific literature, without access to identifiable individual data or intervention involving human subjects. Therefore, approval by a research ethics committee and informed consent are not required, in accordance with applicable regulations and the principles of the Declaration of Helsinki.

- Ethics committee approval: Not applicable.
- Patient informed consent: Not applicable.

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Authors' Contributions

Conceptualization: A.J. Wals Zurita, M.A. González Ruíz.

Methodology: A.J. Wals Zurita, C. Míguez Sánchez.

Software & Formal Analysis: A.J. Wals Zurita.

Validation: J. Pachón Ibáñez, D. Muñoz Carmona, C. Míguez Sánchez.

Investigation: A.J. Wals Zurita, M.A. González Ruíz, G. Campos Rivera.

Writing - Original Draft: A.J. Wals Zurita, M.A. González Ruíz, G. Campos Rivera.

Writing - Review & Editing: All authors.

Supervision: A.J. Wals Zurita.

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