The Pan-Immune-Inflammation Value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE first-line trials

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BACKGROUND: Immune-inflammatory biomarkers (IIBs) showed a prognostic relevance in patients with metastatic CRC (mCRC). We aimed at evaluating the prognostic power of a new comprehensive biomarker, the Pan-Immune-Inflammation Value (PIV), in patients with mCRC receiving first-line therapy.

METHODS: In the present pooled-analysis, we included patients enrolled in the Valentino and TRIBE trials. PIV was calculated as: (neutrophil count × platelet count × monocyte count)/lymphocyte count. A cut-off was determined using the maximally selected rank statistics method. Generalised boosted regression (GBR), the Kaplan–Meier method and Cox hazards regression models were used for survival analyses.

RESULTS: A total of 438 patients were included. Overall, 208 patients (47%) had a low-baseline PIV and 230 (53%) had a high-baseline PIV. Patients with high PIV experienced a worse PFS (HR, 1.66; 95% CI, 1.36–2.03, P < 0.001) and worse OS (HR, 2.01; 95% CI, 1.57–2.57; P < 0.001) compared to patients with low PIV. PIV outperformed the other IIBs in the GBR model and in the multivariable models.

CONCLUSION: PIV is a strong predictor of survival outcomes with better performance than other well-known IIBs in patients with mCRC treated with first-line therapy. PIV should be prospectively validated to better stratify mCRC patients undergoing first-line therapy.

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BACKGROUND

Even in the era of molecular selection,1 a non-negligible fraction of patients with metastatic colorectal cancer (mCRC) receiving first-line treatment has poor outcomes.2 Thus, the identification of new biomarkers for a better prognostic stratification and prediction of treatment outcomes is mandatory. Most of the biomarkers investigated so far are tumour-related, with less focus on host-related factors. Inflammation and immunity play a fundamental role in colorectal cancer initiation and progression,3,4 and several blood-based, easy-to-obtain, immune-inflammatory biomarkers (IIBs) have been investigated in cancer patients.5 Among others, neutrophil-to-lymphocyte ratio (NLR), platelets and monocytes showed a prognostic relevance in the advanced setting,5–8 but the clinical usefulness of such single biomarkers is limited by their low discriminative ability. Since the interplay between immunity, inflammation and cancer relies on complex networks, the use of a composite biomarker encompassing different immune-inflammatory populations and reflecting the global inflammation status could achieve a more robust prognostic power. Of note, the systemic immune-inflammation index (SII) based on lymphocyte, neutrophil and platelet counts, but not monocytes, was first developed for prognostic stratification in patients with hepatocellular carcinoma9 and demonstrated a certain relevance also in mCRC.10

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In patients with mCRC, the use of such IIBs should be assessed in large datasets of patients enrolled in modern trials. In the present pooled-analysis of patients with mCRC receiving first-line therapy in the frame of two randomised academic trials, Valentino and TRIBE, we aimed to evaluate the prognostic power of a new biomarker, the Pan-Immune-Inflammation Value (PIV), including all the immune-inflammatory populations from peripheral blood with a proved prognostic relevance in mCRC.

METHODS

Patients population

The Valentino study (NCT02476045) was a multicentre, randomised, open-label Phase 2 trial that enrolled 229 patients and showed that, in patients with RAS wild-type mCRC, panitumumab plus FOLFOX-4 induction followed by maintenance therapy with single-agent panitumumab (arm B) achieved inferior PFS compared to the same induction regimen followed by panitumumab plus 5-FU/LV (arm A). The TRIBE study (NCT00719797) was a multicentre, randomised, open-label Phase 3 trial by Gruppo Oncologico del Nord Ovest (GONO) that enrolled 508 patients and showed that, in patients with molecularly unselected mCRC, first-line FOLFOXIRI plus bevacizumab achieved superior PFS and OS compared with FOLFIRI plus bevacizumab.

For the present study, we selected patients enrolled in the two trials with available RAS and BRAF mutational status, complete baseline blood-cell count at cycle 1, day 1 (prior to first treatment cycle administration) and clinicopathological data including but not limited to prior exposure to adjuvant chemotherapy, primary tumour resection and primary tumour sidedness.

Statistical analyses

In order to represent a weight of the interaction between inflammatory pro-tumour populations (i.e. neutrophils, platelets and monocytes) and anti-cancer immune populations (i.e. lymphocytes), PIV was calculated as: neutrophil count (10^3/mmc) × platelet count (10^3/mmc) × monocyte count (10^3/mmc)/lymphocyte count (10^3/mmc). Maximaly selected rank statistics method for PFS was used to find an optimal cut-off value to stratify patients in low PIV vs high PIV. NLR was calculated as: neutrophil count (10^3/mmc)/lymphocyte count (10^3/mmc). NLR was defined high if >3, platelet count was defined high if >310 × 10^3/mmc and monocyte count was defined high if >0.5 × 10^3/mmc based on literature data. SII was calculated as: neutrophil count (10^3/mmc) × platelet count (10^3/mmc)/lymphocyte count (10^3/mmc) and defined high if >730 based on literature data. Fisher exact test, Chi-square test, Mann–Whitney test or Kruskal–Wallis test, as appropriate, were used to analyse the association between baseline PIV and the other clinicopathological characteristics. PFS was defined as the time from randomisation to disease progression or death from any cause. OS was defined as the time from randomisation to death from any cause. Generalised boosted regression was used to screen the association of PIV and the other IIBs with PFS and OS. Further survival analyses were performed using the Kaplan–Meier method and the Cox proportional hazards regression models. All the variables showing a P below the significance threshold in the univariate models were included in a multivariable model. The variables showing a P below the significance threshold in the multivariable models were considered to be independent prognostic factors. All tests were 2-sided with a significance threshold of 0.05. Statistical analyses were performed using the R (version 3.5.0) and R Studio (version 1.1.447).

RESULTS

Patients characteristics according to Pan-Immune-Inflammation Value

A total of 438 patients were included in the present analysis: 207 from the Valentino study and 231 from the TRIBE study. The process of patients’ selection is illustrated in Supplementary Fig. S1. In terms of patients’ characteristics, the subsets of patients included in the present study was representative of the overall trial populations (Supplementary Table S1). Median PIV in the entire study population was 417 (IQR, 239–780). The distribution of median PIV according to patients’ and disease characteristics is shown in Supplementary Table S2.

| Table 1. Pan-Immune-Inflammation Value (PIV) according to patients' and disease baseline characteristics. |
|---------------------------------------------------------------|
| Characteristics | Total (N = 438) | PIV low (N = 208) | PIV high (N = 230) | P* |
| Age (years) | | | | 0.111 |
| Median | 62 | 62 | 60 | |
| IQR | 53–68 | 55–68 | 52–67 | |
| Gender | | | | 0.608 |
| Female | 163 (37) | 80 (38) | 83 (36) | |
| Male | 275 (63) | 128 (62) | 147 (64) | |
| ECOG PS | | | | <0.001 |
| 0 | 356 (81) | 186 (89) | 170 (74) | |
| 1 | 82 (19) | 22 (11) | 60 (26) | |
| Prior adjuvant treatment | | | | 0.127 |
| No | 376 (86) | 173 (83) | 203 (88) | |
| Yes | 62 (14) | 35 (17) | 27 (12) | |
| Primary tumour resected | | | | <0.001 |
| No | 133 (30) | 45 (22) | 88 (38) | |
| Yes | 305 (70) | 163 (78) | 142 (62) | |
| Liver-limited disease | | | | 0.066 |
| No | 307 (70) | 137 (66) | 170 (74) | |
| Yes | 131 (30) | 71 (34) | 60 (26) | |
| Synchronous metastases | | | | 0.003 |
| No | 97 (22) | 59 (28) | 38 (17) | |
| Yes | 341 (78) | 149 (72) | 192 (83) | |
| Number of metastatic sites | | | | 0.032 |
| 1 | 181 (41) | 97 (47) | 84 (37) | |
| >1 | 257 (59) | 111 (53) | 146 (63) | |
| Primary tumour sidedness | | | | 0.240 |
| Left | 330 (75) | 162 (78) | 168 (73) | |
| Right | 108 (25) | 46 (22) | 62 (27) | |
| RAS/BRAF status | | | | 0.514 |
| RAS/BRAF wild-type | 276 (63) | 127 (61) | 149 (65) | |
| RAS mut | 146 (33) | 75 (36) | 71 (31) | |
| BRAF mut | 16 (4) | 6 (3) | 10 (4) | |
| Study | | | | 0.659 |
| Valentino | 207 (47) | 112 (54) | 115 (52) | |
| TRIBE | 231 (53) | 96 (46) | 111 (48) | |
| Chemotherapy backbone | | | | 0.324 |
| Doublet | 321 (73) | 157 (75) | 164 (71) | |
| Triplet | 117 (27) | 51 (25) | 66 (29) | |

IQR interquartile range, ECOG Eastern Cooperative Oncology Group, PS performance status, PIV Pan-Immune-Inflammation Value.

*Fisher exact test, Chi-square test, Mann–Whitney test or Kruskal–Wallis test as appropriate. P below the significance threshold are reported in bold.
The optimal cut-off value for PIV using a maximally selected rank statistics method for PFS was 390 (Supplementary Fig. S2). Overall, 208 patients (47%) had a low PIV and 230 (53%) had a high PIV. The distribution of high vs low PIV patients in the two studies was well balanced (Table 1). Compared to patients with low PIV, a higher proportion of patients with high PIV had ECOG PS1 \(P < 0.001\), no primary tumour resection \(P < 0.001\), presence of synchronous metastases \(P = 0.003\) and more than 1 site of metastases \(P = 0.032\) (Table 1). The association between PIV and the classical immune-inflammatory biomarkers is shown in Supplementary Table S3.

| Characteristics | Univariate analysis HR (95% CI) | \(P\) | Multivariable model HR (95% CI) | \(P\) |
|----------------|-------------------------------|------|---------------------------------|------|
| Age (years)\(a\) | 0.291                         | –    |                                 | –    |
| 53 Ref         |                               |      |                                 |      |
| 68 0.92 (0.80–1.07) | –    |      |                                 | –    |
| Gender         | 0.865                         | –    |                                 | –    |
| Female Ref     |                               |      |                                 |      |
| Male 0.98 (0.80–1.21) | –    |      |                                 | –    |
| ECOG PS         | \(0.001\)                     | \(0.002\) |                                 | \(0.002\) |
| 0 Ref          |                               |      |                                 |      |
| 1 1.53 (1.19–1.97) | 1.53 (1.17–1.99) |      |                                 |      |
| Prior adjuvant treatment | \(0.025\) | \(0.580\) |                                 | \(0.580\) |
| No Ref         |                               |      |                                 |      |
| Yes 0.72 (0.54–0.96) | 1.12 (0.75–1.68) |      |                                 |      |
| Primary tumour resected | \(0.009\) | \(0.392\) |                                 | \(0.392\) |
| No Ref         |                               |      |                                 |      |
| Yes 0.75 (0.60–0.93) | 0.90 (0.71–1.15) |      |                                 |      |
| Liver-limited disease | 0.137 | –    |                                 | –    |
| No Ref         |                               |      |                                 |      |
| Yes 0.85 (0.68–1.05) | –    |      |                                 | –    |
| Synchronous metastases | \(<0.001\) | \(0.036\) |                                 | \(0.036\) |
| No Ref         |                               |      |                                 |      |
| Yes 1.55 (1.21–1.98) | 1.46 (1.03–2.09) |      |                                 |      |
| Number of metastatic sites | \(<0.001\) | \(<0.001\) |                                 | \(<0.001\) |
| 1 Ref          |                               |      |                                 |      |
| \(>1\) 1.48 (1.21–1.82) | 1.49 (1.19–1.85) |      |                                 |      |
| Primary tumour sidedness | \(0.005\) | \(0.084\) |                                 | \(0.084\) |
| Left Ref       |                               |      |                                 |      |
| Right 1.39 (1.11–1.74) | 1.24 (0.97–1.59) |      |                                 |      |
| RAS/ BRAF status | \(0.001\) | \(0.015\) |                                 | \(0.015\) |
| RAS/ BRAF wt Ref |                               |      |                                 |      |
| RAS mut 1.18 (0.96–1.46) | 1.07 (0.85–1.34) |      |                                 |      |
| BRAF mut 2.46 (1.48–4.08) | 2.37 (1.40–4.03) |      |                                 |      |
| Study          | 0.784                         | –    |                                 | –    |
| Valentino Ref  |                               |      |                                 |      |
| TRIBE 0.97 (0.79–1.19) | –    |      |                                 | –    |
| Backbone       | 0.485                         | –    |                                 | –    |
| Doublet Ref    |                               |      |                                 |      |
| Triplet 0.92 (0.74–1.15) | –    |      |                                 | –    |
| NLR            | \(0.025\)                     | \(0.462\) |                                 | \(0.462\) |
| Low Ref        |                               |      |                                 |      |
| High 1.26 (1.03–1.54) | 0.89 (0.66–1.21) |      |                                 |      |
| PLT            | \(<0.001\)                    | 0.509 |                                 |      |
| Low Ref        |                               |      |                                 |      |
| High 1.44 (1.18–1.77) | 1.09 (0.84–1.41) |      |                                 |      |

\(\text{Table 2. Cox proportional hazards regression models for PFS.}\)

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Fig. 1 Kaplan–Meier curves for PFS (a) and OS (b) in the overall population according to PIV. Blue lines indicate patients with low PIV whereas yellow lines indicate patients with high PIV. Patients with high PIV had worse survival outcomes compared to patients with low PIV.
Table 2 continued

| Characteristics | Univariate analysis HR (95% CI) | P | Multivariable model HR (95% CI) | P |
|-----------------|---------------------------------|---|---------------------------------|---|
| MONO            |                                 |   |                                 |   |
| Low             | Ref                             |   |                                 |   |
| High            | 1.40 (1.14–1.71)                | 0.001 | 0.98 (0.76–1.26)               | 0.885 |
| SII             |                                 |   |                                 |   |
| Low             | Ref                             |   |                                 |   |
| High            | 1.36 (1.11–1.66)                | <0.001 | 0.97 (0.68–1.38)               | 0.871 |
| PIV             |                                 |   |                                 |   |
| Low             | Ref                             |   |                                 |   |
| High            | 1.66 (1.36–2.03)                | <0.001 | 1.53 (1.09–2.15)               | 0.015 |

*HR hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, PS performance status, Ref reference, NLR neutrophil-to-lymphocyte ratio, PLT platelet count, MONO monocyte count, SII systemic inflammation index, PIV Pan-Immune-Inflammation Value.

A total of 269 OS events were reported during the study period with a pooled median OS of 28.5 months (95% CI, 25.6–31.6). Median OS was 21.6 months (95% CI, 19.9–24.7) for patients with high PIV and 34.4 months (95% CI, 32.1–42.7) for patients with low PIV (HR high vs low, 2.01; 95% CI, 1.57–2.57; P < 0.001) (Fig. 1, panel b). Results were consistent when the two populations were analysed separately (Supplementary Fig. S4). NLR, platelet count, monocyte count and SII were also significantly associated with OS (Table 3). In the generalised boosted regression model, PIV showed the highest relative influence on OS among the immune-inflammatory biomarkers (Fig. 2, panel b). As for PFS, PIV was the only inflammation-based biomarker that showed an independent prognostic impact on OS (adjusted HR high vs low, 1.55; 95% CI, 1.02–2.37; P = 0.042) (Table 3).

Predictive analyses according to Pan-Immune-Inflammation Value

In the *Valentino* study, PIV was not significantly associated with a differential effect of the two maintenance arms in terms of PFS (interaction P = 0.449) and OS (interaction P = 0.612) (Fig. 3, panels a and b, respectively).

Similar results were observed about the predictive role of PIV in the TRIBE study for patients treated with triplet-based vs doublet-based therapy (interaction P for PFS = 0.924; interaction P for OS = 0.951) (Fig. 3, panels C and D). Supplementary Table S4 summarises the results of the predictive analyses.

**DISCUSSION**

In the present pooled-analysis of two first-line trials, we investigated PIV as a new inflammation-based biomarker that integrates NLR, platelet count and monocyte count. PIV demonstrated an extensive and powerful prognostic impact on both PFS and OS in patients with mCRC receiving first-line chemotherapy plus a biological agent. We observed that patients with high baseline PIV had significantly worse survival outcomes compared to patients with low baseline PIV. PIV had the highest relative influence on survival outcomes in the generalised boosted regression models including the other canonical IIBs (i.e. NLR, platelet count, monocyte count) and was the only one that retained an independent prognostic role for PFS and OS in the multivariable models.

To avoid a fragmented information about systemic inflammation, both nomogram systems and scores have been also developed to integrate the various components in the prognostic modelling of CRC, but there is no consensus about the best approach. Rather than analysing the individual contribution of each cellular components (i.e. lymphocytes, neutrophils, platelets and monocytes) on clinical outcomes and then building a calculator (i.e. nomogram or score) in a statistical-driven approach, we tested the prognostic relevance of a new biomarker
incorporating lymphocytes, neutrophils, platelets and monocytes in a way that allowed us to “globally quantify” the cellular compartment of systemic inflammation (i.e. biological-driven approach).

Of note, PIV also outperformed another multicomponent inflammatory index, the SII that does not include information about monocyte count.

Among circulating white blood cells, monocytes are one of the most important subpopulations with an emerging role in cancer progression\(^1\) and potential prognostic impact also in patients with mCRC.\(^7\) Indeed, circulating macrophages represent the primary source of tumour-associated macrophages (TAMs) and the peripheral monocyte count was associated with the density of TAMs in colorectal cancer.\(^18\) Peripheral monocytes are also the source of monocytic (M-) myeloid-derived suppressor cells (MDSCs) that, together with polymorphonuclear (PMN-) MDSCs, characterise a population of immune cells driving immunosuppression and progression in mCRC.\(^9,20\) Of note, PMN-MDSCs are a particular phenotype of circulating neutrophils,\(^21\) so using a biomarker like PIV including monocytes and neutrophils rather than neutrophils only might easily summarise the immunosuppressive contribution of the two components of MDSCs without the need of complex cytfluorimetric analyses.

Even if with some limitations consisting in its retrospective nature and lack of prospective validation, our study included patients enrolled in two randomised clinical trials guaranteeing a high quality of data, especially in weighting the prognostic contribution of monocyte count, a parameter usually not included in the case report forms of clinical studies,\(^22\) particularly academic ones.

In conclusion, our study identifies PIV as a new IIB strongly associated with overall prognosis of mCRC patients receiving first-line treatment and outperforms the other well-known IIBs, suggesting its possible role as a stratification factor in future first-line clinical trials. Further studies should assess the role of PIV as predictive biomarker, particularly regarding its early modifications during treatment as a potentially dynamic biomarker associated with treatment outcomes, and in different settings (for instance, patients with pre-treated mCRC or early stage) or histologies, and with specific regard to immunotherapy approaches.

| Table 3. Cox proportional hazard regression models for OS. |
|----------------------------------------------------------|
| Characteristics | Univariate analysis HR (95% CI) | \(P\) | Multivariable model HR (95% CI) | \(P\) |
| Age (years)\(^a\) | 0.383 | – | – | – |
| 53 | Ref | – | – | – |
| 68 | 1.08 (0.91–1.29) | – | – | – |
| Gender | 0.549 | – | – | – |
| Female | Ref | – | – | – |
| Male | 0.93 (0.73–1.19) | – | – | – |
| ECOG PS | \(<0.001\) | \(<0.001\) | – | – |
| 0 | Ref | Ref | – | – |
| 1 | 1.96 (1.47–2.63) | 2.08 (1.53–2.85) | – | – |
| Prior adjuvant treatment | 0.002 | 0.998 | – | – |
| No | Ref | Ref | – | – |
| Yes | 0.56 (0.38–0.81) | 1.00 (0.57–1.75) | – | – |
| Primary tumour resected | 0.014 | 0.391 | – | – |
| No | Ref | Ref | – | – |
| Yes | 0.72 (0.56–0.94) | 0.88 (0.66–1.18) | – | – |
| Liver-limited disease | 0.151 | – | – | – |
| No | Ref | – | – | – |
| Yes | 0.82 (0.63–1.07) | – | – | – |
| Synchronous metastases | \(<0.001\) | 0.043 | – | – |
| No | Ref | Ref | – | – |
| Yes | 1.87 (1.36–2.57) | 1.63 (1.02–2.61) | – | – |
| Number of metastatic sites | 0.001 | 0.009 | – | – |
| 1 | Ref | Ref | – | – |
| \(>1\) | 1.51 (1.17–1.95) | 1.43 (1.09–1.88) | – | – |
| Primary tumour sidedness | 0.001 | 0.014 | – | – |
| Left | Ref | Ref | – | – |
| Right | 1.56 (1.20–2.03) | 1.42 (1.08–1.88) | – | – |
| RAS/BRaf status | \(<0.001\) | 0.003 | – | – |
| RAS/BRaf wt | Ref | Ref | – | – |
| RAS mut | 1.36 (1.06–1.74) | 1.29 (0.99–1.69) | – | – |
| BRAF mut | 2.88 (1.72–4.84) | 2.65 (1.55–4.54) | – | – |
| Study | 0.497 | – | – | – |
| Valentino | Ref | – | – | – |
| TRIBE | 0.91 (0.70–1.19) | – | – | – |
| Backbone | 0.789 | – | – | – |
| Doublet | Ref | – | – | – |
| Triplet | 1.04 (0.80–1.34) | – | – | – |
| NLR | \(<0.001\) | 0.402 | – | – |
| Low | Ref | Ref | – | – |
| High | 1.56 (1.23–1.99) | 1.17 (0.81–1.68) | – | – |
| PLT | \(<0.001\) | 0.168 | – | – |
| Low | Ref | Ref | – | – |
| High | 1.67 (1.31–2.12) | 1.23 (0.92–1.64) | – | – |

| Table 3 continued |
|----------------------------------------------------------|
| Characteristics | Univariate analysis HR (95% CI) | \(P\) | Multivariable model HR (95% CI) | \(P\) |
| MONO | \(0.001\) | 0.691 | – | – |
| Low | Ref | Ref | – | – |
| High | 1.52 (1.19–1.94) | 0.94 (0.70–1.27) | – | – |
| SII | \(<0.001\) | 0.677 | – | – |
| Low | Ref | Ref | – | – |
| High | 1.58 (1.24–2.01) | 0.91 (0.59–1.41) | – | – |
| PIV | \(<0.001\) | 0.042 | – | – |
| Low | Ref | Ref | – | – |
| High | 2.01 (1.57–2.57) | 1.55 (1.02–2.37) | – | – |

HR hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, PS performance status, Reference, NLR neutrophil-to-lymphocyte ratio, PLT platelet count, MONO monocyte count, SII systemic inflammation index, PIV Pan-Immune-Inflammation Value.

\(^a\)The two values represent the first and third quartile, respectively, of the variable distribution.
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Fig. 3  Kaplan–Meier curve for PFS and OS according to PIV and treatment arm in the Valentino study (a and b, respectively) and in the TRIBE study (c and d, respectively). PIV was not significantly associated with a differential effect of the two maintenance arms in the Valentino study nor with a differential effect of triplet-based vs doublet-based therapy in the TRIBE study.

AUTHOR CONTRIBUTIONS
G.F.: conceptualisation, data curation, formal analysis, investigation, writing of the original draft, review/editing and approval of the final manuscript. V.G.: data curation, investigation, review/editing and approval of the final manuscript. C.A.: data curation, investigation, review editing and approval of the final manuscript. F.Mo.: investigation, review/editing and approval of the final manuscript. R.Mo.: investigation, review/editing and approval of the final manuscript. S.C.: data curation, investigation, review/editing and approval of the final manuscript. F.Ma.: data curation, investigation, review/editing and approval of the final manuscript. S.L.: investigation, review/editing and approval of the final manuscript. A.S.B.: investigation, review/editing and approval of the final manuscript. M.T.: investigation, review/editing and approval of the final manuscript. S.B.: investigation, review/editing and approval of the final manuscript. M.C.: investigation, review/editing and approval of the final manuscript. A.B.: investigation, review/editing and approval of the final manuscript. R.Mu.: investigation, review/editing and approval of the final manuscript. A.Z.: investigation, review/editing and approval of the final manuscript. G.Tom.: investigation, review/editing and approval of the final manuscript. F.L.: investigation, review/editing and approval of the final manuscript. G.Ton.: investigation, review/editing and approval of the final manuscript. E.C.: investigation, review/editing and approval of the final manuscript. F.d.B.: investigation, review/editing and approval of the final manuscript. C.C.: conceptualisation, data curation, investigation, review/editing and approval of the final manuscript. F.P.: conceptualisation, data curation, formal analysis, investigation, supervision, writing of the original draft, review/editing and approval of the final manuscript.

ADDITIONAL INFORMATION
Ethics approval and consent to participate Institutional review board and ethics committee approval was obtained from all participating centres. All the patients provided written informed consent before any study-related procedures. The study was conducted in accordance with the Declaration of Helsinki.
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