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# REAL-WORLD INSIGHTS INTO THE PREVALENCE AND PROGNOSTIC SIGNIFICANCE OF TROPHOBLAST CELL-SURFACE ANTIGEN 2 AND FOLATE RECEPTOR ALPHA IN UTERINE CARCINOSARCOMA

**Rio de Janeiro**
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Trabalho de Conclusão de Curso apresentado ao Instituto Nacional de Câncer como requisito parcial para a conclusão do Programa de Residência Médica em Oncologia Clínica.

Orientadora: Prof.ª Dra. Andreia Cristina de Melo

Revisão: Prof.ª Dra. Shirley Burburan

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## RESUMO

ALBUQUERQUE, Lucas Zanetti de. **Dados de mundo real da prevalência e papel prognóstico do antígeno 2 de superfície celular trofoblástica e receptor de folato alfa em carcinossarcoma uterino**. Trabalho de Conclusão de Curso (Residência Médica em Oncologia) — Instituto Nacional de Câncer (INCA), Rio de Janeiro, 2025.

Carcinossarcoma uterino (CSU) é um raro e agressivo tumor ginecológico e a descrição de biomarcadores imuno-histoquímicos que ajudem a guiar terapias alvo nessa doença é uma lacuna crítica na pesquisa médica. Esse estudo objetiva medir a prevalência do antígeno 2 de superfície celular trofoblástica (Trop-2) e do receptor de folato alfa (FRα) em CSU e avaliar seu papel prognóstico. Essa análise retrospectiva avaliou dados de mulheres diagnosticadas com CSU submetidas a cirurgia seguida de quimioterapia (carboplatina e paclitaxel) entre janeiro de 2012 e dezembro de 2020. Microarranjos teciduais de 89 amostras foram avaliados. Alta positividade foi definida como escore ≥ 50% de células tumorais com intensidade de coloração forte para Trop-2 e ≥ 75% com intensidade de coloração moderada ou forte para FRα. A média de idade ao diagnóstico foi de 66,2 anos (desvio padrão 7) e o índice de massa corporal médio foi de 28,7 kg/m² (DP 6,2). Mulheres não-brancas corresponderam a 71,6% dos casos. Alta expressão de Trop-2 e FRα foi observada em 49,4% e 17,4% dos componentes epiteliais, respectivamente, com nenhuma alta expressão no componente sarcomatoso. Superexpressão de FRα correlacionou-se com superexpressão de Trop-2 ($p$=0,007). Em análises multivariadas, estadio avançado ($p$=0,015) e ressecção incompleta ($p$<0,001) foram preditivos para menor sobrevida livre de progressão, enquanto ambos fatores também se correlacionaram com pior sobrevida global ($p$=0,013 e $p$=0,001, respectivamente). FRα e Trop-2 são progressivamente reconhecidos como alvos terapêuticos e a expressão em níveis elevados no componente epitelial de CSU é promissora, apesar de não associada a prognóstico nessa coorte.



Palavras-chave: carcinossarcoma uterino; biomarcadores; antígeno 2 de superfície celular trofoblástica; receptor de folato alfa.

## ABSTRACT

ALBUQUERQUE, Lucas Zanetti de. **Real-world insights into the prevalence and prognostic significance of trophoblast cell-surface antigen 2 and folate receptor alpha in uterine carcinosarcoma.** Final paper (Medical Residency in Clinical Oncology) — Brazilian National Cancer Institute (INCA), Rio de Janeiro, 2026.

Uterine carcinosarcomas (UCS) are rare and aggressive gynecological tumors and the description of immunohistochemical biomarkers that can help guide targeted treatments in this disease is a critical gap in current medical research. This study aims to measure the prevalence of trophoblast cell-surface antigen 2 (Trop-2) and folate receptor alpha (FRα) in UCS and evaluate their prognostic significance. This retrospective analysis examined data from female patients diagnosed with UCS who underwent surgery followed by carboplatin and paclitaxel chemotherapy between January 2012 and December 2020. Tissue microarrays from 89 samples were assessed. High positivity was defined as a score of ≥ 50% of tumor cells with strong staining intensity for Trop-2 and ≥ 75% with medium or strong staining intensity for FRα. The mean age at diagnosis was 66.2 years (Standard Deviation, SD: 7) and the mean body mass index was 28.7 kg/m² (SD: 6.2). Non-white women accounted for 71.6% of cases. High expression of Trop-2 and FRα was found in 49.4% and 17.4% of epithelial components, respectively, with no high positivity in sarcomatous components. FRα overexpression correlated with Trop-2 overexpression ($p = 0.007$). On multivariate analysis, advanced stage ($p = 0.015$) and incomplete resection ($p < 0.001$) predicted shorter progression-free survival, while both factors also independently worsened overall survival ($p = 0.013$ and $p = 0.001$, respectively). FRα and Trop-2 are increasingly recognized as therapeutic targets and their elevated expression levels in the epithelial component of UCS are promising, although not associated with prognosis in this cohort.



Keywords: uterine carcinosarcoma; biomarkers; folate receptor alpha; trophoblast cell-surface antigen 2.

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RESEARCH

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# Real-world insights into the prevalence and prognostic significance of trophoblast cell-surface antigen 2 and folate receptor alpha in uterine carcinosarcoma

Lucas Zanetti de Albuquerque[1†], Jessé Lopes da Silva[1†], Fabiana Resende Rodrigues[2], Priscila Valverde Fernandes[2], Isabele Ávila Small[1], Luís Felipe Leite[1], Gustavo Guitmann[3] and Andreia Cristina de Melo[1*]

## Abstract

**Background** Uterine carcinosarcomas (UCS) are rare and aggressive gynecological tumors and the description of biomarkers that can help guide targeted treatments in this disease is a critical gap in current medical research. This study aims to measure the prevalence of trophoblast cell-surface antigen 2 (Trop-2) and folate receptor alpha (FRα) in UCS and evaluate their prognostic significance.

**Methods** This retrospective analysis examined data from female patients diagnosed with UCS who underwent surgery followed by carboplatin and paclitaxel chemotherapy between January 2012 and December 2020. Tissue microarrays from 89 samples were assessed for Trop-2 and FRα expression by IHC. High positivity was defined as a score of ≥ 50% of tumor cells with strong staining intensity for Trop-2 and ≥ 75% with medium or strong staining intensity for FRα. Sociodemographic and clinical features were analyzed alongside progression-free survival (PFS) and overall survival (OS) outcomes.

**Results** The mean age at diagnosis was 66.2 years (Standard Deviation, SD: 7) and the mean body mass index was 28.7 kg/m$^2$ (SD: 6.2). Non-white women accounted for 71.6% of cases. Heterologous subtype corresponded to 63.0% of cases, and lymphovascular invasion was observed in 59.2%. Complete resection (R0) was achieved in 66.3% of cases. High expression of Trop-2 and FRα was found in 49.4% and 17.4% of epithelial components, respectively, with no high positivity in sarcomatous components. Negative margins were more common in stage I/II disease ($p = 0.001$), and FRα overexpression correlated with Trop-2 overexpression ($p = 0.007$). On multivariate analysis, advanced stage ($p = 0.015$) and incomplete resection ($p < 0.001$) predicted shorter PFS, while both factors also independently worsened OS ($p = 0.013$ and $p = 0.001$, respectively). Lymphadenectomy was associated with improved OS ($p = 0.025$).

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**Conclusion** Complete resection and advanced stage were suggested as prognostic factors in UCS. FRα and Trop-2 are increasingly recognized as therapeutic targets and their elevated expression levels in the epithelial component of UCS are promising, although not associated with prognosis in this cohort.

**Keywords** Uterine carcinosarcoma, Biomarkers, Folate receptor alpha, Trophoblast cell-surface antigen 2

## Background

Uterine carcinosarcomas (UCS) are rare and aggressive gynecological tumors distinguished by biphasic histology comprising epithelial and sarcomatous components, the latter classified as homologous or heterologous according to histopathological characteristics [1, 2]. This unique morphological structure places UCS as an important model for investigating the mechanisms underlying epithelial-mesenchymal transition (EMT). EMT is a critical biological process wherein tumor cells undergo a loss of cell polarity and disruption of intercellular junctions, accompanied by cytoskeletal reorganization. These cellular transformations enhance migratory capabilities and facilitate metastasis, thereby contributing to the malignancy associated with UCS [3]. Both tumor aggressiveness and rarity hinder the assessment of new therapeutic strategies and often exclude patients from trials, resulting in a significant clinical gap [4].

Trophoblast cell-surface antigen 2 (Trop-2) is a transmembrane glycoprotein encoded by the *TACSTD2* gene, which has upregulated expression in various malignancies while remaining low or absent in normal tissues [5–7]. Trop-2 has a critical role in promoting cancer cell proliferation, invasion and metastasis in some tumor types [8–10]. Clinically, elevated Trop-2 levels have been associated with poor overall survival (OS) and increased tumor aggressiveness, notably in endometrial cancer, where overexpression results in higher recurrence rates [11–13]. As a predictive biomarker, Trop-2 expression has been linked with response to targeted therapies, such as sacituzumab govitecan, an antibody-drug conjugate (ADC) designed to target Trop-2. Treatment efficacy has been observed even in tumors with varying Trop-2 expression, suggesting its utility in guiding therapeutic strategies [14, 15].

Folate receptor α (FRα) is a cell-surface glycoprotein encoded by the *FOLR1* gene, with an important role in regulating cellular processes such as proliferation and invasion [16]. It has a restricted expression pattern in normal tissues in parallel to a marked presence in different cancer types [17, 18] and is considered an important prognostic and predictive biomarker in various cancers, including gynecologic carcinosarcomas and ovarian cancer. A FRα expression pattern is consistently observed across gynecologic malignancies, including ovarian and uterine carcinosarcoma, where the majority of specimens seem to exhibit positivity for this biomarker [19, 20]. Despite this widespread expression, studies indicate that FRα-high expression does not correlate with prognostic outcomes in UCS, as it lacks a significant association with clinicopathological features or survival rates [20]. Conversely, meta-analyses have linked high FRα expression to poor OS in other malignancies, underscoring its potential role as a predictive marker for treatment resistance [21]. FRα also serves as a biomarker guiding therapeutic strategies, as high expression levels are essential to point patients that might benefit from treatment with mirvetuximab soravtansine, an ADC that targets FRα [22].

ADCs are an expanding class of cancer treatment that can selectively deliver a toxic payload to tumor cells by targeting specific surface biomarkers, thereby minimizing systemic toxicity. They are composed of monoclonal antibodies conjugated to cytotoxic drug molecules by a chemical linker, and their mechanisms of action drive a more selective delivery of chemotherapeutic agents to cancer cells, aiming for better treatment tolerability and effectiveness [23]. The low expression level of both Trop-2 and FRα in normal tissues and their high expression in malignancies make them promising targets for several biomarker-directed anti-cancer therapies designed to exploit those receptors' abundance in cancer cells, such as ADCs [24].

Investigating available biomarkers with meaningful clinical relevance for managing UCS remains a critical gap in current medical research. Likewise, reports on UCS immunohistochemical (IHC) characterization on such important biomarkers are scarce and their association with prognosis remains unclear. This study focused on assessing Trop-2 and FRα expression levels in UCS, while also examining the prognostic and therapeutic implications of both biomarkers. Furthermore, potential associations between biomarker expression profiles and various clinicopathological parameters were explored to elucidate their clinical relevance in patients diagnosed with UCS.

## Materials and methods

### Study design, patient selection and data collection

This study received approval from the Ethics in Human Research Committee of the Brazilian National Cancer Institute (INCA) in Rio de Janeiro, Brazil, and was conducted according to the Good Clinical Practice guidelines. The authors adhered closely to the recommendations outlined in the STrengthening the Reporting

of Observational Studies in Epidemiology (STROBE) guideline [25].

A comprehensive institutional database review identified women diagnosed with UCS who underwent surgery followed by postoperative chemotherapy with the standard regimen of carboplatin and paclitaxel (CP) administered every three weeks for six cycles [26, 27] at INCA between January 2012 and December 2021. Patients with insufficient or inadequate pathological samples, as well as those presenting synchronous or metachronous tumors, were excluded from the study. Relevant clinical data, including sociodemographic factors, staging, surgical interventions, histological subtype (homologous versus heterologous), tumor progression, and survival outcomes, were retrospectively extracted from the medical records. Staging was conducted following the criteria established by the International Federation of Gynecology and Obstetrics (FIGO, 2009) [28].

### Immunohistochemistry

The construction of the tissue microarray (TMA) was performed using regions exhibiting the highest tumor cellularity in formalin-fixed, paraffin-embedded samples of primary tumors. Each specimen featured six 4-µm core punches that ensured adequate representation of both sarcomatous and epithelial areas. The staining of tumor cells was evaluated against negative controls obtained through hematoxylin counterstaining and positive controls. Additionally, the slides were quantitatively assessed based on the ratio of positive cells to the total number of cells.

The assessment of Trop-2 expression by immunohistochemistry (clone EP431, Cell Marque, 1:400 dilution) utilized a scoring system that integrated both staining intensity and the proportion of tumor cells exhibiting positivity. Staining intensity was categorized on a four-point scale: 0 indicated absence of staining, 1 + denoted weak membranous staining, 2 + reflected medium staining, and 3 + represented strong membranous staining. The analysis emphasized the percentage of tumor cells with strong (3+) membranous staining, with thresholds defined as negative (0%), low (1–10%), moderate (11–50%), and high (51–100%). For FRα (clone EPR20277, Abcam, 1:1000 dilution), the evaluation was based on the percentage of viable tumor cells showing membranous staining, which was scored from 0 (none) to 3+ (strong). FRα positivity was stratified into negative (0–24%), low (25–49%), moderate (50–74%), and high (≥ 75%) based on the proportion of cells exhibiting ≥ 2 + staining intensity, with a minimum of 100 viable tumor cells necessary for accurate assessment.

### Statistical analysis

Progression-free survival (PFS) was defined as the time from the onset of CP to the first instance of disease progression, recurrence, or death, and OS was measured from the first CP infusion to death from any cause, with women alive at the last data collection point censored. The Kaplan-Meier method was used to estimate overall PFS and OS, while also stratifying by age, body mass index (BMI), race, omentectomy status, residual disease, lymphovascular invasion (LVI), histological subtype, cancer stage, adjuvant radiotherapy and IHC marker status. Continuous variables were tested for normality using the Shapiro-Wilk test, and categorical variables were presented as absolute and relative frequencies.

To assess the association of the IHC markers status and clinicopathological features with staging, the Student's t-test and chi-square were used. The crude Hazard Ratio (HR) for each variable was calculated by Cox proportional hazards. A multiple Cox proportional hazards model was conducted utilizing the stepwise approach, whereby variables identified as significant in the univariate analysis were sequentially incorporated into the model, and only those that retained statistical significance were included in the final analysis. A p-value < 0.05 was considered statistically significant. The missing data was excluded from the analysis. The statistical analyses were conducted using the R project version 4.4.0 [29].

## Results

Data from the 89 women included in this retrospective cohort were described in Table 1. The mean age by the time of diagnosis was 66.2 years (Standard Deviation, SD 7.0) and the mean observed BMI was 28.7 kg/m² (SD 6.2). Most of the patients were ≥ 60 years old (77.5%), postmenopausal (97.8%) and non-white (71.6%). Advanced disease on diagnosis (FIGO III/IV) was observed in 76.4% of the patients. The heterologous subtype was predominant (63.0%), and LVI was observed in 59.2% of cases, with missing data on 18.0% and 20.2% of the cases for these features, respectively (Additional file 1). There was no association between staging at diagnosis and the IHC expression status for both biomarkers (Additional file 2).

In the epithelial component, high Trop-2 expression was found in 49.4%, while high FRα expression was observed in 17.4% of cases. In contrast, the sarcomatous component showed no high expression for either marker (Fig. 1). Additionally, high FRα expression correlated with high Trop-2 expression ($p = 0.007$) (Table 2). Representative images of staining intensity scores for each biomarker are shown in Fig. 2.

Regarding surgical treatment, all patients underwent total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO), while omentectomy and

**Table 1** Clinical-pathological characteristics and clinical stage

| Variables/Biomarkers | I and II (%) | III and IV (%) | Total (%) | Crude *p*-value |
|---|---|---|---|---|
| Number of patients (%) | 21 (23.6) | 68 (76.4) | 89 (100.0) | - |
| Mean age, years (SD) | 66.1 (8.3) | 66.2 (6.6) | 66.2 (7.0) | 0.923 |
| 60-year-old cutoff | | | | |
| < 60 years old | 7 (33.3) | 13 (19.1) | 20 (22.5) | 0.287 |
| ≥ 60 years old | 14 (66.7) | 55 (80.9) | 69 (77.5) | - |
| Menopausal status | | | | |
| Postmenopausal | 20 (95.2) | 67 (98.5) | 87 (97.8) | 0.962 |
| Premenopausal | 1 (4.8) | 1 (1.5) | 2 (2.2) | - |
| Mean BMI kg/m$^2$ (SD) | 28.2 (7.2) | 28.8 (5.9) | 28.7 (6.2) | 0.688 |
| Race/Ethnicity | | | | |
| Non-white | 14 (66.7) | 49 (73.1) | 63 (71.6) | 0.767 |
| White | 7 (33.3) | 18 (26.9) | 25 (28.4) | - |
| Histologic subtype | | | | |
| Heterologous | 7 (41.2) | 39 (69.6) | 46 (63.0) | 0.065 |
| Homologous | 10 (58.8) | 17 (30.4) | 27 (37.0) | - |
| LVI | | | | |
| Absent | 9 (56.2) | 20 (36.4) | 29 (40.8) | 0.256 |
| Present | 7 (43.8) | 35 (63.6) | 42 (59.2) | - |

*Abbreviations*: *BMI* Body mass index, *SD* Standard deviation, *LVI* Lymphovascular invasion

**Table 2** Correlation between Trop-2 and FRα expression in the epithelial component of UCS

| | | FRα (dependent) | | OR (univariable) | OR (multivariable) |
|---|---|---|---|---|---|
| | | High | Negative/low/moderate | | |
| Trop-2 | High | 13 (31.0) | 29 (69.0) | - | - |
| | negative/low/moderate | 1 (2.4) | 40 (97.6) | 17.93 (3.29–334.89.29.89, $p$ = 0.007) | 17.93 (3.29–334.89.29.89, $p$ = 0.007) |

Number in data frame = 89, Number in model = 83, Missing = 6, AIC = 65.4, C-statistic = 0.754, H&L = Chi-sq (8) 0.00 ($p$ = 1.000)

*Abbreviations*: *OR* Odds ratio

lymphadenectomy were also carried out in 44.9% and 66.3% of patients, respectively (Table 3). Complete resection (R0) was achieved in 66.3% of cases, with 51.1% of patients receiving adjuvant radiotherapy thereafter.

The median follow-up for the overall population was 55 months (95% CI: 43.0–74.0), during which 65 patients experienced disease progression or death. The median PFS was 15 months (95% CI: 11.0–23.0). Patients with FIGO stages I/II did not reach a median PFS, while those with stages III/IV had a median PFS of 11.5 months (95% CI: 8.0–19.0). Univariate analysis indicated that advanced stage (III/IV) (HR 3.88, 95% CI: 1.82–8.27, $p$ < 0.001)

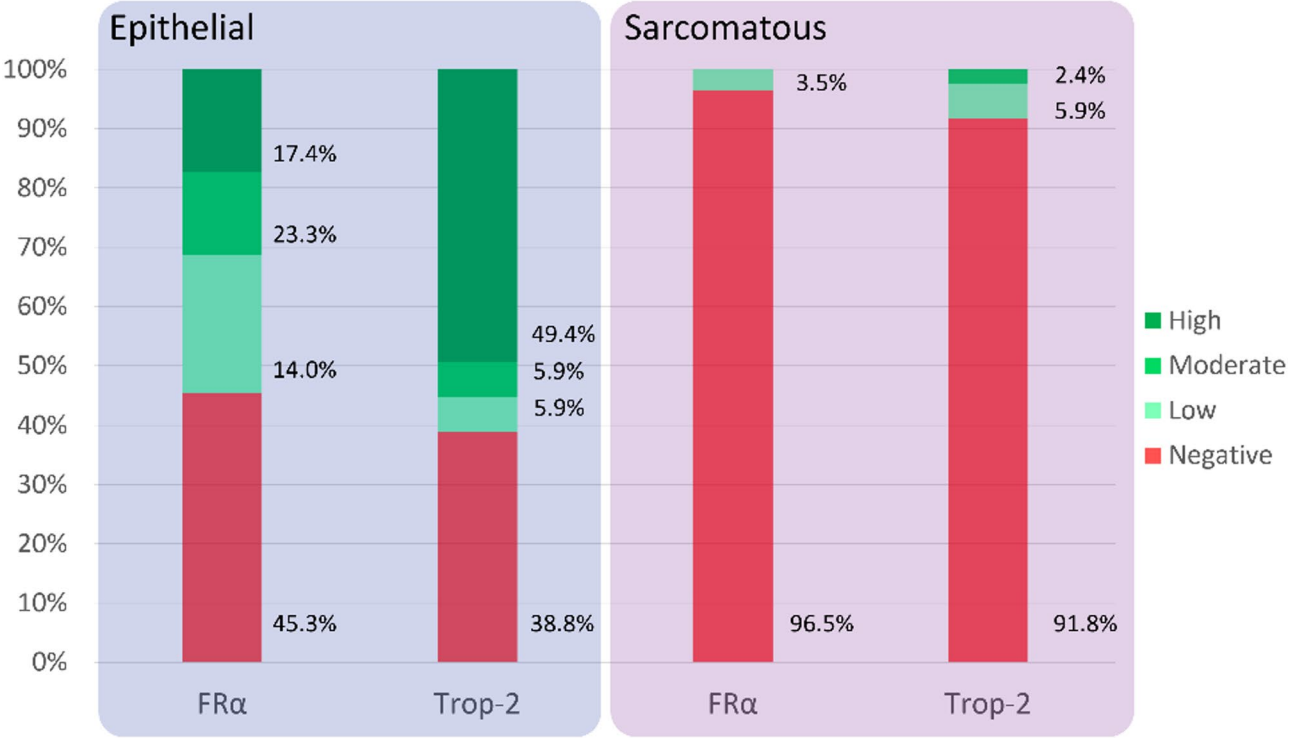


**Fig. 1** Graphic representation of the immunohistochemistry biomarkers staining. IHQ positivity, grading from negative to low, moderate and high expression, is demonstrated for both FRα and Trop-2 on epithelial and sarcomatous components of UCS

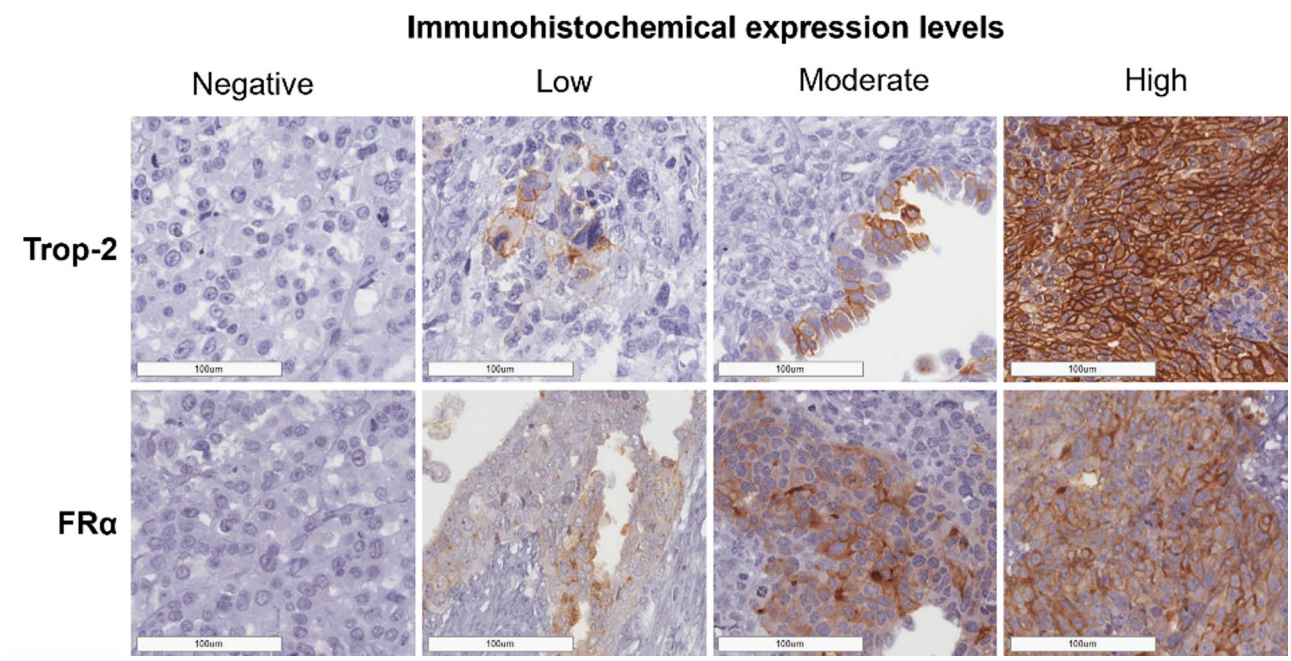


**Fig. 2** Immunohistochemistry staining representation of Trop-2 and FRα expression on the epithelial component of UCS. The images were captured at a magnification of x20 to ensure precision

**Table 3** Cohort's treatment characteristics

| Treatment/Variable | I and II (%) | III and IV (%) | Total (%) | Crude *p*-value |
|---|---|---|---|---|
| Type of surgery | | | | |
| TAH + BSO | 11 (52.4) | 38 (55.9) | 49 (55.1) | 0.975 |
| TAH + BSO + Omentectomy | 10 (47.6) | 30 (44.1) | 40 (44.9) | - |
| Lymphadenectomy | | | | |
| No | 5 (23.8) | 25 (36.8) | 30 (33.7) | 0.404 |
| Yes | 16 (76.2) | 43 (63.2) | 59 (66.3) | - |
| Resection status | | | | |
| R0 | 21 (100.0) | 38 (55.9) | 59 (66.3) | 0.001 |
| R1/2 | 0 (0.0) | 30 (44.1) | 30 (33.7) | - |
| Adjuvant radiotherapy | | | | |
| No | 6 (28.6) | 37 (55.2) | 43 (48.9) | 0.060 |
| Yes | 15 (71.4) | 30 (44.8) | 45 (51.1) | - |

*Abbreviations*: *R0* Complete resection (defined as residual disease inferior to 1.0 cm), *R1/2* Residual cancer at the primary site or regional lymph nodes, *TAH + BSO* Total abdominal hysterectomy and bilateral salpingo-oophorectomy

and incomplete resection (R1/R2) were associated with poorer PFS (HR 4.68, 95% CI: 2.72–8.03, $p < 0.001$). In contrast, lymphadenectomy (HR 0.45, 95% CI: 0.27–0.75, $p = 0.002$) and adjuvant radiotherapy (HR 0.50, 95% CI: 0.30–0.83, $p = 0.007$) were linked to improved PFS. There was no significant association between Trop-2 or FRα expression and PFS. By multivariate analysis, advanced disease stages III/IV (HR 2.70, 95% CI: 1.21–6.01, $p = 0.015$) and incomplete resection (HR 3.57, 95% CI: 2.04–6.23, $p < 0.001$) had a significantly negative impact on PFS (Fig. 3; Table 4).

The median OS was 20 months (95% CI: 15.0–33.0) for the overall population, with a five-year OS rate of 21.7% (95% CI: 13.4–35.1%) and 64 reported deaths. Patients with stages I/II did not achieve median OS (95% CI: 57.0 - not reached (NR)), while those with stages III/IV had a median OS of 17.0 months (95% CI: 13.0–28.0). Univariate analysis showed that incomplete resection was linked to poorer median OS (HR 4.43, 95% CI: 2.60–7.52, $p < 0.001$), while lymphadenectomy (HR 0.42, 95% CI 0.25–0.70, $p = 0.001$) and adjuvant radiotherapy (HR 0.53, 95% CI: 0.32–0.89, $p = 0.015$) were associated with improved OS. No significant association was observed between Trop-2 or FRα expression and OS. Multivariate analysis showed that advanced stages III/IV (HR 2.83, 95% CI: 1.25–6.42, $p = 0.013$) and incomplete resection (HR 2.77, 95% CI: 1.54–4.99, $p = 0.001$) increased the risk of death, while lymphadenectomy improved OS (HR 0.53, 95% CI: 0.31–0.93, $p = 0.025$) (Fig. 4; Table 5).

As shown in Fig. 5, a swimmer plot depicts the survival trajectories of patients, highlighting the timing of treatment, disease progression, and transition to palliative care. Additionally, alternative stratifications of Trop-2 and FRα expression by tumor component and their effects on PFS and OS are shown in Additional file 3.

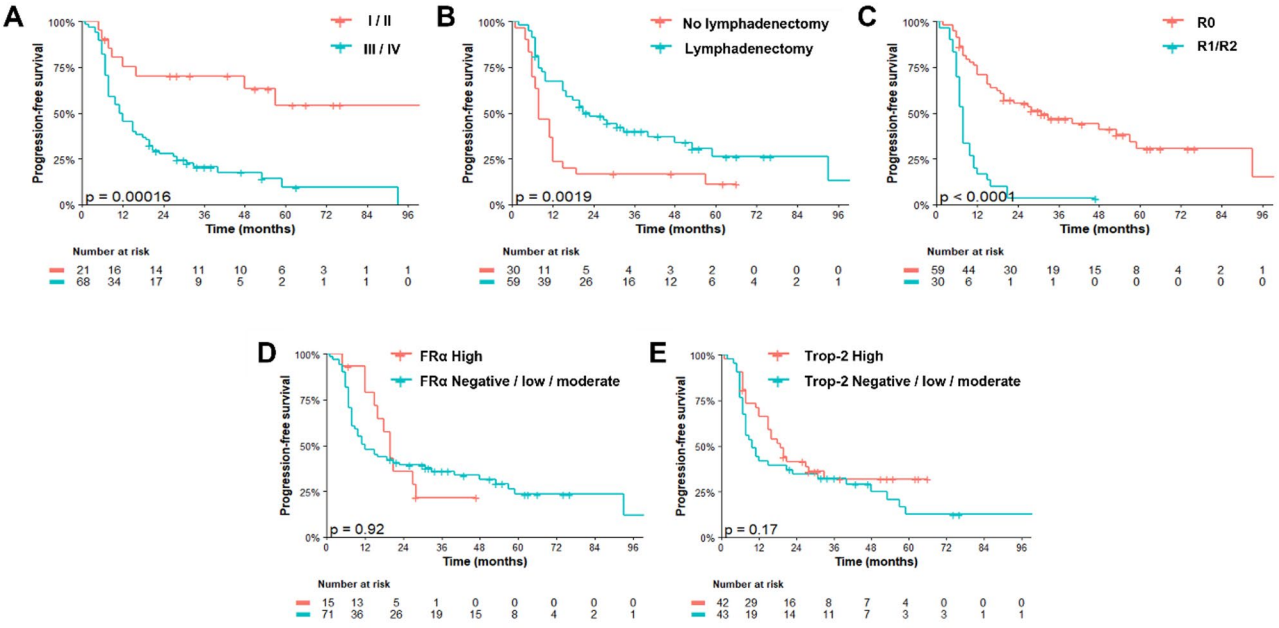


**Fig. 3** Progression-free survival (PFS). PFS by stage (**A**), lymphadenectomy (**B**), residual disease status (**C**) and dichotomized (high versus negative, low and moderate) immunohistochemistry expression levels of FRα (**D**) and Trop-2 (**E**) on the epithelial component of UCS. Margin status after surgery was stratified according to the size of residual disease into R0 (without residual disease, inferior to 1.0 cm in size), R1 (microscopic residual disease) and R2 (macroscopic residual disease). As for immunohistochemistry markers, Kaplan Meier curves for PFS were stratified by the cut-off points previously set up and divided into negative, low, moderate versus high positivity expression of both biomarkers. Tick marks indicate censored data

## Discussion

In this retrospective analysis of Brazilian women diagnosed with UCS, IHC assessment revealed significant expression discrepancies for the biomarkers Trop-2 and FRα between epithelial and sarcomatous components, as the sarcomatous elements had predominantly negative staining. No association was found between Trop-2 and FRα expression and survival outcomes. The cohort primarily consisted of non-white women over 60 years old, aligning with data from the Surveillance, Epidemiology, and End Results (SEER) program [30, 31]. High rates of advanced disease and lymphovascular invasion were observed, along with an unexpected proportion of heterologous sarcomatous components, possibly indicating regional diagnostic variations. These findings are consistent with previous studies, including those by Matsuo et al. [19, 31–33], highlighting the prevalence of advanced-stage disease in this population.

Previous studies have documented high Trop-2 expression levels in nearly one-third of samples, indicating a notable prevalence [34]. A comprehensive IHC analysis of 42 UCS samples showed high expression of Trop-2 in a considerable proportion of cases, with strong and moderate expression in 28.6% and 23.8% of the UCS cases, respectively [35]. In the current cohort, almost half of the samples exhibited high expression of Trop-2 in the epithelial component. Differences in findings across studies may be attributed to variations in methodologies. Hence, in the context of non-standardized positivity thresholds and variable scoring methods [13, 36], this study focused on categorizing samples according to the most strong membrane staining (3+) and the proportion of tumor cells bearing this characteristic, ensuring the representation of high Trop-2 expressing tumors. Trop-2 expression might also be influenced by additional tumor features, as other studies demonstrated that driver *KRAS* mutations were associated with Trop-2 high expression in pancreatic and colorectal cancer [37].

The expression level of Trop-2 has emerged as a significant prognostic indicator in several malignancies, correlating with poorer OS, particularly in gynecologic and gastrointestinal cancers [38–43]. A systematic review further established a negative association between high expression of Trop-2 and OS outcome across multiple solid tumors, with a pooled HR of 1.89 [42]. Additionally, the impact of Trop-2 high expression on clinical outcomes seems to be affected by co-occurring mutations; for instance, microsatellite-stable colorectal cancers have shown worse OS when associated with high expression of Trop-2 [37]. However, in the current UCS cohort, high expression of Trop-2 did not significantly impact clinical outcomes or prognosis.

Given the relatively high prevalence of Trop-2 expression in UCS, it presents a promising target for innovative ADC therapies. Sacituzumab govitecan, an ADC consisting of an IgG1 monoclonal antibody targeting Trop-2

**Table 4** Crude and adjusted hazards ratios for carcinosarcoma progression-free survival (PFS) by univariate and multivariate analysis

| Clinicopathological features | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p*-value | HR | 95% CI | *p*-value |
| Mean age, years (SD) | 1.01 | 0.98–1.05 | 0.393 | - | - | - |
| Mean BMI kg/m$^2$ (SD) | 1.00 | 0.96–1.04 | 0.891 | - | - | - |
| Race/Ethnicity (White vs. non-white) | 1.13 | 0.66–1.93 | 0.662 | - | - | - |
| **Clinical stage (III/IV vs. I/II)** | **3.88** | **1.82–8.27** | **< 0.001** | **2.70** | **1.21–6.01** | **0.015** |
| Omentectomy (yes vs. no) | 0.91 | 0.56–1.48 | 0.704 | - | - | - |
| **Resection status (R1/2 vs. R0)** | **4.68** | **2.72–8.03** | **< 0.001** | **3.57** | **2.04–6.23** | **< 0.001** |
| **Lymphadenectomy (yes vs. no)** | **0.45** | **0.27–0.75** | **0.002** | - | - | - |
| **Adjuvant radiotherapy (yes vs. no)** | **0.50** | **0.30–0.83** | **0.007** | - | - | - |
| LVI (present vs. absent) | 0.96 | 0.55–1.68 | 0.879 | - | - | - |
| Histological subtype (homologous vs. heterologous) | 0.68 | 0.38–1.22 | 0.198 | - | - | - |
| FRα IHC expression intensity (epithelial component) (negative/low/moderate vs. high) | 1.05 | 0.54–2.03 | 0.889 | - | - | - |
| Trop-2 IHC expression intensity (epithelial component) (negative/low/moderate vs. high) | 1.43 | 0.86–2.37 | 0.168 | - | - | - |
| FRα IHC expression (epithelial component) | | | | | | |
| High | Ref. | - | - | - | - | - |
| Moderate | 1.01 | 0.41–2.53 | 0.977 | - | - | - |
| Low | 1.35 | 0.62–2.95 | 0.451 | - | - | - |
| Negative | 0.93 | 0.45–1.90 | 0.841 | - | - | - |
| Trop-2 IHC expression (epithelial component) | | | | | | |
| High | Ref. | - | - | - | - | - |
| Moderate | 1.78 | 0.62–5.12 | 0.286 | - | - | - |
| **Low** | **3.15** | **1.20–8.26** | **0.019** | - | - | - |
| Negative | 1.25 | 0.73–2.17 | 0.416 | - | - | - |
| FRα IHC expression (sarcomatous component) | | | | | | |
| Low | Ref. | - | - | - | - | - |
| Negative | 0.56 | 0.17–1.80 | 0.327 | - | - | - |
| Trop-2 IHC expression (sarcomatous component) | | | | | | |
| Low | Ref. | - | - | - | - | - |
| Moderate | 1.47 | 0.15–14.31 | 0.741 | - | - | - |
| Negative | 2.04 | 0.63–6.61 | 0.236 | - | - | - |

Statistically significant results are in bold

*Abbreviations: BMI* Body mass index, *SD* Standard deviation

linked to an active irinotecan metabolite, has been shown to have considerable efficacy and has received FDA approval for the treatment of advanced solid tumors [44]. Significant objective response rates to sacituzumab govitecan have been demonstrated in clinical trials regardless of Trop-2 expression levels. Notably, benefits have been observed in studies focused on hormone receptor-positive HER2-negative breast cancer and pretreated metastatic triple-negative breast cancer, with a trend toward greater efficacy noted in patients exhibiting high expression of Trop-2 [45, 46].

Another investigational ADC, datopotamab deruxtecan (Dato-DXd), has been shown to have the potential for treating high-grade serous ovarian cancer, with promising preclinical activity against tumors that exhibit high expression of Trop-2 [47]. In a phase II study, Dato-DXd demonstrated antitumor effectiveness in patients with advanced endometrial cancers who had previously failed platinum chemotherapy, achieving notable objective response rates within a diverse cohort, including patients with carcinosarcoma [48].

Saito et al. [20] assessed FRα expression in a cohort of 120 patients with UCS using IHC characterization with a four-tiered expression system. Their findings indicated that 20% of the samples exhibited high expression levels, closely aligning with the 17.4% observed in the present study. Hanley et al. [49] reported FRα positivity in 87% of 46 UCS cases, employing a more inclusive definition of positivity (≥ 5% of tumor cells at any intensity) and a different antibody clone (Mab26B3). Such methodological differences likely account for the variations in FRα expression rates. This cohort IHC analysis also showed that FRα high expression levels were associated to similar Trop-2 high expression, pointing to a possible co-expression association of both biomarkers when in high levels.

The association between FRα expression and the histological type of the epithelial component of UCS remains inconsistent across studies. Some investigations have found no significant correlation [20], while others have

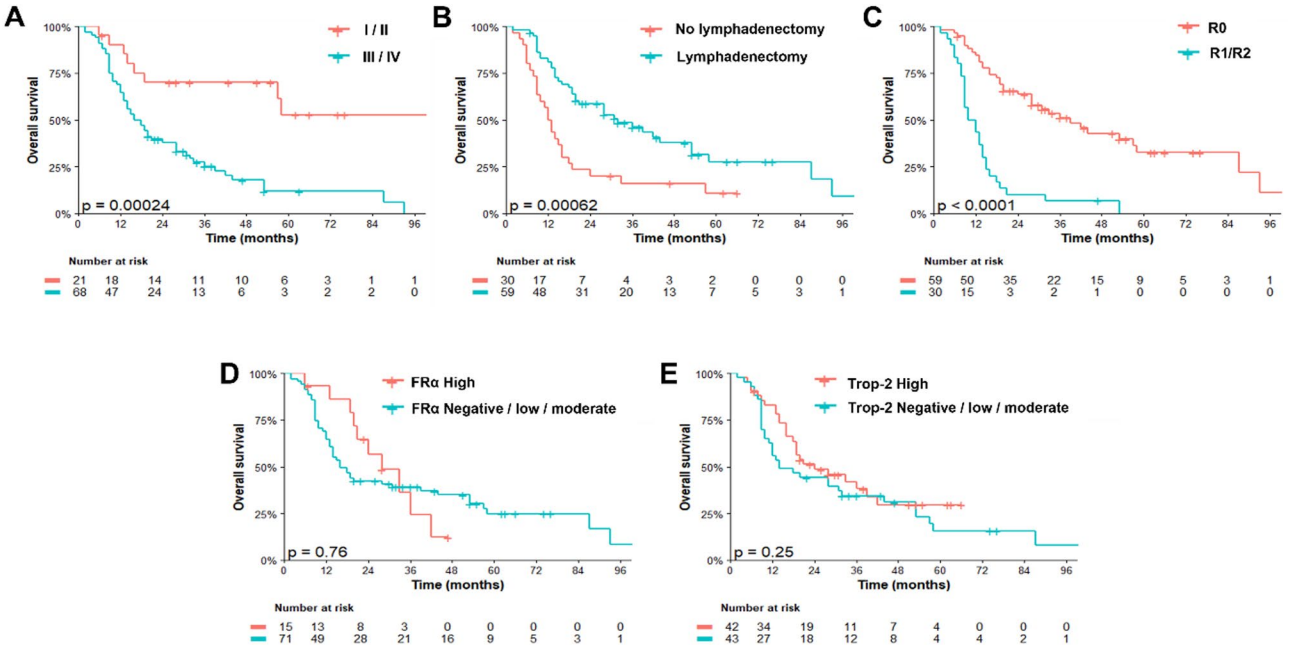


**Fig. 4** Overall survival (OS). OS by stage (**A**), lymphadenectomy (**B**), residual disease status (**C**) and dichotomized (high versus negative, low and moderate) immunohistochemistry expression levels of FRα (**D**) and Trop-2 (**E**) on the epithelial component of UCS. Margin status after surgery was stratified according to the size of residual disease into R0 (without residual disease, inferior to 1.0 cm in size), R1 (microscopic residual disease) and R2 (macroscopic residual disease). As for immunohistochemistry markers, Kaplan Meier curves for OS were stratified by the cut-off points previously set up and divided into negative, low, moderate versus high positivity expression of both biomarkers. Tick marks indicate censored data

noted enhanced FRα staining in serous and high-grade endometrial cancers [49]. This study did not explore the histological subclassification of the UCS epithelial component, thus precluding any correlation analyses. Notably, 96.5% of samples in this study exhibited a lack of FRα expression in the sarcomatous component, corroborating previous findings that showed only 4.3% of samples demonstrated weak staining in this area [49].

In gynecologic malignancies, studies indicate that FRα-positive patients represent the majority, with positivity rates ranging from 80% to 100% [20]. However, various factors, including the type of anti-FRα antibody, positivity thresholds, and scoring methods, can influence these results. The optimal timing for assessing FRα expression is still debated; testing conducted early may not capture evolving molecular characteristics due to treatment [50]. Some research suggests that FRα expression remains consistent over time and is not affected by prior therapies [51, 52]. Furthermore, the biopsy site, whether from a primary or metastatic tumor, and inter- and intratumoral heterogeneity may impact FRα evaluations. A real-world analysis of patients with ovarian, fallopian tube, and primary peritoneal cancers demonstrated higher FRα expression in primary tissues compared to metastatic sites, emphasizing the necessity for comprehensive biomarker testing and the challenges presented by tumor heterogeneity [53].

Regarding clinical outcomes, Saito et al. [20] found no significant association between high FRα expression levels and PFS or OS (HR 0.87, 95% CI: 0.83–1.58; $p$ = 0.628). Similarly, the present cohort revealed no impact of FRα expression on survival. However, conflicting evidence persists; a systematic review including 4,471 patients indicated that high FRα expression is predictive of poor OS (HR 0.78, 95% CI: 0.64–0.94; $p$ = 0.009), particularly in subgroups of high-expressing endometrial cancers (HR 1.30, 95% CI: 1.05–1.61) [21]. Therefore, the necessity for a standardized method to evaluate FRα expression is clear.

Current studies primarily focus on ovarian cancer, leading to a gap in understanding the role of FRα as a predictive factor for the efficacy of anti-FRα therapies [24]. Mirvetuximab soravtansine (MIRV), a pioneering ADC targeting FRα, consists of an IgG1 monoclonal antibody linked to a tubulin-targeting agent [51]. The phase III MIRASOL trial revealed substantial improvements in treatment responses among women with high FRα expression, defined as 75% or more of viable tumor cells showing moderate to strong staining. Patients with FRα high expression treated with MIRV achieved an objective response rate of 42.3%, compared to only 15.9% in those receiving standard chemotherapy. This significant disparity highlights the potential of FRα as a predictive biomarker, suggesting that effective targeting of this receptor can confer considerable therapeutic advantages for

**Table 5** Crude and adjusted hazards ratios for carcinosarcoma overall survival (OS) by univariate and multivariate analysis

| Clinicopathological features | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p*-value | HR | 95% CI | *p*-value |
| Mean age, years (SD) | 1.02 | 0.99–1.06 | 0.209 | - | - | - |
| Mean BMI kg/m$^2$ (SD) | 0.99 | 0.96–1.03 | 0.794 | - | - | - |
| Race/Ethnicity (White vs. non-white) | 1.10 | 0.64–1.89 | 0.729 | - | - | - |
| **Clinical stage (III/IV vs. I/II)** | **3.78** | **1.77–8.06** | **0.001** | **2.83** | **1.25–6.42** | **0.013** |
| Omentectomy (yes vs. no) | 0.92 | 0.56–1.51 | 0.731 | - | - | - |
| **Resection status (R1/2 vs. R0)** | **4.43** | **2.60–7.52** | **< 0.001** | **2.77** | **1.54–4.99** | **0.001** |
| **Lymphadenectomy (yes vs. no)** | **0.42** | **0.25–0.70** | **0.001** | **0.53** | **0.31–0.93** | **0.025** |
| **Adjuvant radiotherapy (yes vs. no)** | **0.53** | **0.32–0.89** | **0.015** | - | - | - |
| LVI (present vs. absent) | 1.01 | 0.57–1.79 | 0.984 | - | - | - |
| Histological subtype (homologous vs. heterologous) | 0.67 | 0.38–1.20 | 0.176 | - | - | - |
| FRα IHC expression intensity (epithelial component) (negative/low/moderate vs. high) | 1.13 | 0.57–2.24 | 0.734 | - | - | - |
| Trop-2 IHC expression intensity (epithelial component) (negative/low/moderate vs. high) | 1.36 | 0.81–2.28 | 0.244 | - | - | - |
| FRα IHC expression (epithelial component) | | | | | | |
| High | Ref. | - | - | - | - | - |
| Moderate | 1.04 | 0.41–2.66 | 0.927 | - | - | - |
| Low | 1.54 | 0.69–3.45 | 0.292 | - | - | - |
| Negative | 0.99 | 0.47–2.07 | 0.971 | - | - | - |
| Trop-2 IHC expression (epithelial component) | | | | | | |
| High | Ref. | - | - | - | - | - |
| Moderate | 2.20 | 0.76–6.38 | 0.147 | - | - | - |
| Low | 1.98 | 0.76–5.17 | 0.164 | - | - | - |
| Negative | 1.20 | 0.69–2.10 | 0.514 | - | - | - |
| FRα IHC expression (sarcomatous component) | | | | | | |
| Low | Ref. | - | - | - | - | - |
| Negative | 0.76 | 0.18–3.14 | 0.704 | - | - | - |
| Trop-2 IHC expression (sarcomatous component) | | | | | | |
| Low | Ref. | - | - | - | - | - |
| Moderate | 1.65 | 0.17–16.18 | 0.667 | - | - | - |
| Negative | 2.29 | 0.70–7.50 | 0.171 | - | - | - |

Statistically significant results are in bold

*Abbreviations: BMI* Body mass index, *SD* Standard deviation

patients with FRα-positive tumors [22]. The consistency of the MIRASOL trial findings influenced the choice of a similar scoring method for this study (although using a different IHC antibody) over other previously described evaluation methods [20].

Both advanced clinical stage (III/IV) and incomplete resection (R1/R2) were the main factors statistically associated with poorer PFS and OS. The negative influence of those factors on the prognosis has already been demonstrated in other UCS studies [54–57]. Lymphadenectomy was associated with better OS, which was also shown by a population analysis performed on the SEER database [58]. This finding might relate to the importance of achieving complete gross resection to improve survival, as demonstrated by Tanner et al., [57] who reported the significant impact of optimal cytoreduction on median OS in UCS (52 versus 9 months, $p < 0.0001$).

The strengths of this study are primarily attributed to its innovative and comprehensive assessment of Trop-2 and FRα frequency in UCS and its impact on survival outcomes. Given the rarity of this disease, this cohort successfully gathered a significant number of cases, which enhances the robustness of the findings. Stringent inclusion criteria ensured the selection of cases with consistent characteristics providing a homogenous population, thereby improving the evaluation of how clinicopathological features influence disease progression and survival outcomes. Surgical samples were meticulously reviewed by two experienced pathologists, and results were synthesized through multivariate analyses, enhancing the internal validity of the study.

However, this research is not without limitations, particularly due to its retrospective nature. This design may blind some important confounding variables, potentially impacting the overall quality of the analysis altogether with the influence of some missing data. The relatively small sample size might pose a barrier to ensure adequate power to detect slight differences in survival related to the evaluated biomarkers. Additionally, the variability of methodologies applied to assess both Trop-2 and FRα

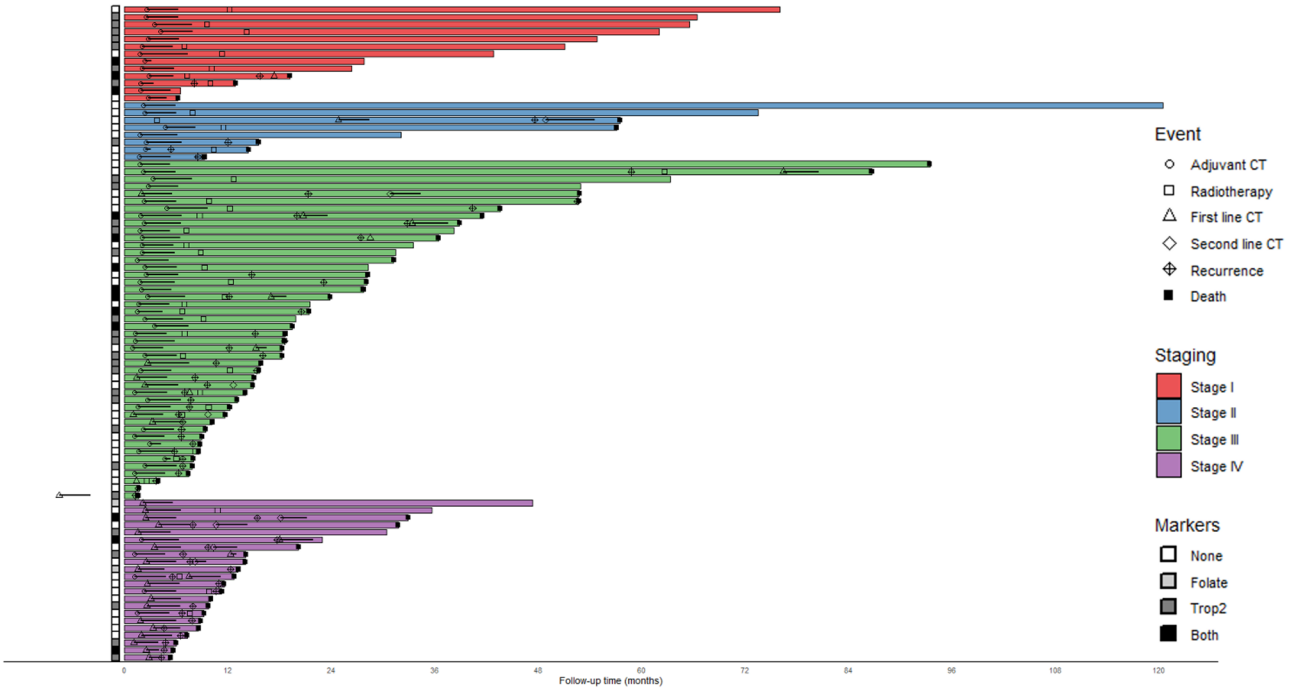


**Fig. 5** Swimmer plot highlighting important timepoints on patients' follow-up. Swimmer plot depicts disease assessments relevant to curative treatment, recurrence and palliative chemotherapy, highlighting patients with high FRα and/or Trop-2 expression. Each horizontal bar represents an individual patient. The timeline is aligned by the date of surgery, and key clinical milestones are annotated for each case

IHC expression among different reports might hinder precise comparisons between the results of this study and previously published data. The use of a TMA-based IHC analyses can possibly also increase the vulnerability of this study to inaccurate results due to tumor intrinsic heterogeneity. Molecular analyses were not performed within the scope of this study, and treatment decisions regarding multimodal adjuvant therapies, such as chemotherapy followed by radiotherapy, were left to the discretion of the treating clinicians. Finally, the focus on a single public institution might limit the generalizability of the findings, considering the limitations of access to gold-standard treatments.

## Conclusion

This study identified elevated Trop-2 and FRα expression predominantly within the epithelial component of UCS, whereas expression in sarcomatous components was minimal. Despite their notable prevalence, no association was found between these biomarkers and patient survival outcomes. The key prognostic factors identified were advanced clinical stage and incomplete surgical resection. Given the high positivity of Trop-2 and FRα, these biomarkers represent promising targets for innovative precision therapies, highlighting the need for prospective clinical trials to further explore biomarker-directed treatment approaches in UCS.

**Abbreviations**

| | |
|---|---|
| ADC | Antibody-drug conjugate |
| BMI | Body mass index |
| BSO | Bilateral salpingo-oophorectomy |
| CP | Carboplatin and paclitaxel |
| Dato-DXd | Datopotamab deruxtecan |
| EMT | Epithelial-mesenchymal transition |
| FRα | Folate receptor alpha |
| GCP | Good Clinical Practice |
| HR | Hazard Ratio |
| ICH | International Council for Harmonisation |
| IHC | Immunohistochemical |
| INCA | Brazilian National Cancer Institute |
| LVI | Lymphovascular invasion |
| MIRV | Mirvetuximab soravtansine |
| NR | Not reached |
| OS | Overall survival |
| PFS | Progression-free survival |
| SD | Standard Deviation |
| STROBE | Strengthening the reporting of observational studies in epidemiology |
| TAH | Total abdominal hysterectomy |
| TMA | Tissue microarray |
| Trop-2 | Trophoblast cell-surface antigen 2 |
| UCS | Uterine carcinosarcomas |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-15298-z.

Additional file 1. Clinical-pathological characteristics, treatment description and Immunohistochemistry analysis of FRα and Trop-2 by histologic component of uterine carcinosarcoma including missing data.

Additional file 2. Immunohistochemistry analysis of FRα and Trop-2 by histologic component of uterine carcinosarcoma and stage.

Additional file 3. PFS and OS analyses according to alternative stratifications of Trop-2 and FRα expression across epithelial and sarcomatous tumor components.

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**Authors' contributions**
JLS, ACM worked on the conceptualization of the study. The methodology was planned by JLS, FRR, PVF, IAS, ACM. Data curation and formal analysis was perfomed by LZA, JLS, IAS, LFLS and data verification was carried out by LZA, JLS, ACM. The project administration and supervision counted with LZA, JLS, ACM, which also wrote the original draft. All authors read, reviewed and approved the final manuscript and had final responsibility for the decision to submit for publication.

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**Data availability**
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
Ethics approval was obtained from the Institutional Review Board (Ethics Committee for Human Research of the Brazilian National Cancer Institute), under registration number 03727818.2.0000.5274. The study was conducted in accordance with the Good Clinical Practice (GCP) guidelines established by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). It was also aligned with core principles from the 2000 version of the Declaration of Helsinki, as referenced by Brazilian Resolution No. 466/2012 of the National Health Council, which regulates research involving human subjects in Brazil. Given the retrospective observational design of this study, the committee waived the requirement for obtaining informed consent from all participants.

**Consent for publication**
Not applicable.

**Competing interests**
ACM has received grants or contracts from Amgen, AstraZeneca, Bristol Myers Squibb, Clovis Oncology, GSK, MSD, Novartis, Pierre Fabre, Regeneron Pharmaceuticals, and Roche, with payments made to the institution. ACM also reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Adium, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, GSK, MSD, Novartis, and Roche. The other authors declare that they have no conflicts of interest.

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