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Original Research Article

Axillary de-escalation after neoadjuvant chemotherapy for advanced lymph node involvement in breast cancer

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ABSTRACT

Introduction: Sentinel lymph node biopsy reduces morbidity in patients with clinically node-positive breast cancer who achieve axillary pathologic complete response following neoadjuvant therapy (NACT). De-escalation trials primarily addressed cN1 disease, with underrepresentation of cN2 disease. This study evaluates the role of de-escalation in patients with cN2 breast cancer.
Methods: A retrospective analysis of the National Cancer Database (2013–2020) included women over 18 with T1-2 invasive breast cancer and clinical N2 disease who received NACT followed by ALND or SLNB then ALND. The primary outcome was pathologic nodal status post-NACT.
Results: Of 5852 cN2 patients treated, 18.15 % achieved ypN0, 0.97 % had isolated tumor cells, 19.14 % were ypN1, 49.64 % were ypN2, and 12.20 % were ypN3 following NACT. Achieving ypN0 was associated with pCR in the breast, HER2-positive and triple-negative receptor status, cT2 tumors, and younger age.
Conclusion: Despite some patients with cN2 disease achieving ypN0, most exhibited residual axillary disease post-NACT. These findings indicate that axillary de-escalation may not be feasible for most patients with cN2 disease, underscoring the importance of meticulous patient selection and assessment.

1. Introduction

Axillary lymph node dissection (ALND) has traditionally been important for both staging and regional control in managing the axilla in patients diagnosed with clinically node-positive breast cancer.[1,2] However, ALND can lead to significant morbidity, including musculoskeletal pain, limited range of motion, nerve injury, seroma formation, and lymphedema.[3–7]

Sentinel lymph node (SLNB) surgery provides important staging information with less morbidity compared to ALND in patients with clinically node-negative breast cancer; however, it was not initially deemed suitable for patients with clinically node-positive disease. The landmark ACOSOG Z0011 trial established the oncologic safety of omitting ALND in clinically node-negative patients with limited sentinel node involvement who were undergoing breast-conserving therapy.[8,9] However, ACOSOG Z0011 only applied to patients having upfront surgery. The practice of omitting ALND has been extended to include clinically node-positive patients who convert to ypN0 following neoadjuvant chemotherapy (NACT). De-escalation of axillary surgery involves omitting axillary lymph node dissection (ALND) in favor of sentinel lymph node biopsy (SLNB) and targeted axillary dissection (TAD), following the conversion of clinically node-positive (cN+) status to clinically node-negative (cN0) after neoadjuvant therapy. Axillary de-escalation strategies in breast cancer aim to reduce the potential morbidity associated with ALND.

Various prospective clinical trials have explored the feasibility of SLNB following neoadjuvant therapy in patients with clinically node-positive disease. In the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial, the false negative rate (FNR) of SLNB following neoadjuvant chemotherapy (NACT) was 12.6 %, but decreased to 10.8 % with the use of both blue dye and radiolabeled colloid, and to 9.1 % with the examination of at least three SLNBs. The multicenter SN FNAC trial

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reported an FNR of 8.4 % with immunohistochemistry, compared to 13.3 % without its use. Concurrently, MD Anderson introduced targeted axillary dissection (TAD), which involves removing both the SLNBs and the clipped lymph node, achieving an FNR of 2.0 %. Similarly, the Netherlands' MARI procedure, which marks the axillary lymph node with a radioactive seed, reported a 7 % FNR. However, the majority of these studies included patients with cN1 disease predominantly, while those with cN2 disease were underrepresented constituting only 5 % and 6 % of patients in the ACOSOG 1071 and SN FNAC trials, respectively.[12–14] The AJCC 8th Edition Cancer Staging Manual[15] defines cN2 as metastasis in ipsilateral level I or II axillary lymph nodes that are clinically fixed or matted, or metastasis in clinically detected ipsilateral internal mammary nodes without clinically evident axillary lymph node involvement. The 2019 St. Gallen conference panel concluded that for patients with clinically positive nodes that downstage to clinically negative after NACT, SLNB surgery might be appropriate. Recommendations suggested that SLNB biopsy could replace ALND if three or more SLNBs are found and all are negative, or if TAD is performed, including clipping positive nodes at diagnosis.[10] However, the panel stated that patients with cN2 disease should still undergo complete axillary dissection and regional nodal irradiation, regardless of their response to NACT.[10,11]

Although there is a trend toward de-escalating axillary surgery in select patients with clinically node-positive disease following NACT, the appropriateness of this strategy for patients with cN2 disease remains uncertain. This uncertainty is largely due to the underrepresentation of these patients in prior trials, which restricts our understanding of whether omitting ALND is advisable for this particular patient cohort.[16–18]

This study aims to inform understanding of the applicability of axillary surgery de-escalation strategies for cN2 breast cancer through the analysis of a comprehensive dataset of this distinct patient group.

2. Methods

2.1. Data source

The National Cancer Database (NCDB), a joint effort of the American College of Surgeons and the American Cancer Society, was queried for this study. The NCDB is a de-identified hospital-based registry database that captures more than 70 % of all newly diagnosed cancers in the United States.[19] The institutional review board deemed this study exempt.

2.2. Patients

A retrospective analysis of the National Cancer Database was conducted from 2013 to 2020. This study timeframe provides a contemporary dataset to analyze clinical trends and outcomes related to axillary management.

Inclusion criteria for the study were female patients over 18 years old with cT1-2 invasive breast cancer and clinical cN2 disease, all undergoing neoadjuvant chemotherapy followed by either upfront ALND or ALND after sentinel lymph node biopsy (SLNB). Patients who did not undergo axillary surgery, those with stage IV disease, those with incomplete data on neoadjuvant chemotherapy or surgical outcomes were excluded from the study.

Importantly, all participants ultimately underwent ALND, regardless of their initial surgical treatment approach, to ensure accuracy in nodal assessment and avoid potential false negatives associated with SLN alone. The selection of cT1-T2 categories aligns with those used in axillary de-escalation prospective clinical trials.

2.3. Outcome measures

The primary outcome was the final pathologic status of the axillary nodes following neoadjuvant chemotherapy (e.g., ypN). Breast pathologic complete response (pCR) was defined as ypT0 or ypTis, while nodal pCR was defined as ypN0. Data were collected on patient demographics and tumor characteristics, including pathologic nodal status, tumor grade, histology, receptor status, and breast tumor response.

2.4. Statistical analysis

Descriptive statistics were performed to examine possible patient and tumor characteristics related to the primary outcome. Chi-square test was used to assess differences in categorical variables. Descriptive statistics were used to summarize the study cohort according to demographic data, tumor characteristics, and treatment modality. A univariable logistic regression analysis was initially performed to study the risk ratios associated with downstaging to ypN0. A multivariable logistic regression model was then fit to analyze patient and tumor factors associated with ypN0 status in patients undergoing ALND. The odds ratio (OR) and 95 % confidence interval (CI) were calculated for each variable. All statistical analyses were performed with STATA BE 17.0 (StataCorp), and a p-value lower than 0.05 was considered statistically significant.

3. Results

The examined cohort consisted of 5852 women with cN2 breast cancer who underwent NACT followed by either upfront ALND or ALND following SLNB. Among these patients, 1062 (18.15 %) achieved nodal pCR (ypN0), 57 (0.97 %) had residual ITCs, 1120 (19.14 %) were ypN1, 2905 (49.64 %) were ypN2, and 714 (12.20 %) were ypN3. The baseline study population and tumor characteristics stratified by axillary nodal response are shown in Table 1.

Patients achieving ypN0 status demonstrated distinct characteristics. They were primarily aged between 40 and 69 years, with a notable majority in the 40–54 age group (39.6 %) compared to those below the age of 40 (16.8 %) and those above the age of 70 (8.1 %).

When examining tumor characteristics, invasive ductal carcinoma (IDC) was the histologic subtype present in 90.7 % of patients who achieved ypN0 response, compared to 1.8 % with invasive lobular carcinoma (ILC) and 1.9 % with IDC + ILC histological characteristics. Poorly differentiated tumors comprised 70.8 % of cases achieving ypN0, compared to 18 % with moderately differentiated tumors, and only 1.4 % with well differentiated tumors.

Among patients who achieved nodal pCR (ypN0), 63 % also had a pCR in the primary breast tumor (ypT0, ypTis) while 22.1 % had a ypT1 stage, 6.5 % with ypT2 and 0.5 % had ypT3 stage.

In the univariable analysis, several associations were identified in patients who had pCR and achieved ypN0 response and are illustrated in Table 2. Younger patients (40–54 years) were more likely to achieve ypN0 (OR 0.66; CI 0.53–0.81; p-value <0.001), compared to those aged between 55 and 69 (OR 0.47; CI 0.38–0.58; p-value<0.001) and those over 70 (OR 0.30; CI 0.22–0.39; p-value<0.001). When analyzing histological types, IDC was more likely to achieve ypN0 compared to ILC alone and IDC with ILC features (OR 0.17; CI 0.11–0.28; p-value <0.001 and OR 0.36; CI 0.23–0.58; p-value <0.001, respectively). Poorly differentiated tumors were more likely to achieve ypN0 (OR 5.15; CI 3.03–8.74; p-value <0.001), followed by moderately differentiated tumors (OR 1.78; CI 1.03–3.07; p-value = 0.037). Nodal response demonstrated a strong association with ypT0 and ypTis (OR 17.79; CI 14.50–21.82; p-value <0.001 and OR 10.57; CI 7.00–15.96; p-value<0.001, respectively), whereas residual pathological breast disease was less likely to achieve ypN0. Receptor status was also associated with ypN0 response. Specifically, HR-/HER2+ showing significant association with ypN0 (OR 11.05; CI 8.79–13.89; p-value <0.001), followed by HR-/HER2- (OR 5.09; CI 4.21–6.16; p-value <0.001) and HR+/HER2+ (OR 4.52; CI 3.68–5.54; p-value <0.001).

The multivariable analysis, as detailed in Table 3, revealed several key factors associated with axillary nodal response. Age continued to show statistical significance for achieving ypN0 in younger patients

Table 1
Study cohort characteristics.

N = 5852	pN0 (18.15 %) (N = 1062)	ITCs (0.97 %) (N = 57)	pN1 (19.14 %) (N = 1120)	pN2 (49.64 %) (N = 2905)	pN3 (12.20 %) (N = 714)
Age of patient					
<40	178 (16.8 %)	8 (14.1 %)	151 (13.4 %)	237 (8.2 %)	55 (7.7 %)
40–54	421 (39.6 %)	21 (36.8 %)	426 (38.1 %)	965 (33.2 %)	201 (28.1 %)
55–69	377 (35.5 %)	22 (38.6 %)	429 (38.3 %)	1242 (42.7 %)	315 (44.1 %)
70+	86 (8.1 %)	6 (10.5 %)	114 (10.2 %)	461 (15.9 %)	143 (20.1 %)
Ethnicity					
White	782 (73.6 %)	40 (70.2 %)	785 (70.1 %)	2214 (76.2 %)	574 (80.4 %)
Black	197 (18.6 %)	14 (24.6 %)	256 (22.8 %)	492 (16.9 %)	100 (14 %)
Other/Unknown	83 (7.8 %)	3 (5.2 %)	79 (7.1 %)	199 (6.9 %)	40 (5.6 %)
Histology					
IDC	964 (90.7 %)	45 (79 %)	1001 (89.3 %)	2419 (83.3 %)	532 (74.5 %)
ILC	19 (1.8 %)	7 (12.2 %)	37 (3.3 %)	276 (9.5 %)	122 (17.1 %)
IDC + ILC	20 (1.9 %)	4 (7 %)	40 (3.6 %)	141 (4.8 %)	42 (5.9 %)
Other	59 (5.6 %)	1 (1.8 %)	42 (3.8 %)	69 (2.4 %)	18 (2.5 %)
Grade					
Well differentiated	15 (1.4 %)	1 (1.8 %)	42 (3.8 %)	154 (5.3 %)	32 (4.5 %)
Moderately differentiated	191 (18 %)	15 (26.3 %)	344 (30.7 %)	1054 (36.2 %)	225 (31.5 %)
Poorly differentiated	752 (70.8 %)	30 (52.6 %)	600 (53.6 %)	1266 (43.6 %)	335 (46.9 %)
Missing/ Unknown	104 (9.8 %)	11 (19.3 %)	134 (11.9 %)	431 (14.9 %)	122 (17.1 %)
Clinical T stage					
cT1	239 (22.5 %)	15 (26.3 %)	249 (22.2 %)	736 (25.3 %)	198 (27.7 %)
cT2	823 (77.5 %)	42 (73.7 %)	871 (77.8 %)	2169 (74.7 %)	516 (72.3 %)
Pathologic T stage					
ypT0	604 (56.9 %)	13 (22.8 %)	131 (11.7 %)	77 (2.6 %)	11 (1.5 %)
ypTIS	65 (6.1 %)	2 (3.5 %)	17 (1.5 %)	18 (0.7 %)	5 (0.7 %)
ypT1	235 (22.1 %)	26 (45.6 %)	536 (47.8 %)	849 (29.2 %)	197 (27.6 %)
ypT2	69 (6.5 %)	10 (17.6 %)	298 (26.6 %)	1513 (52.1 %)	299 (41.9 %)
ypT3	5 (0.5 %)	0 (0 %)	28 (2.5 %)	99 (3.4 %)	87 (12.2 %)
ypT4	2 (0.2 %)	0 (0 %)	4 (0.4 %)	31 (1.1 %)	19 (2.7 %)
Unknown	82 (7.7 %)	6 (10.5 %)	106 (9.5 %)	318 (10.9 %)	96 (13.4 %)
Receptor status					
HR-/HER2-	327 (30.8 %)	15 (26.3 %)	247 (22.1 %)	389 (13.4 %)	116 (16.2 %)
HR+/HER2+	238 (22.4 %)	18 (31.6 %)	196 (17.5 %)	342 (11.8 %)	73 (10.2 %)
HR-/HER2+	227 (21.4 %)	2 (3.5 %)	75 (6.7 %)	145 (5 %)	24 (3.4 %)
HR+/HER2-	213 (20.1 %)	16 (28.1 %)	503 (44.9 %)	1642 (56.5 %)	384 (53.8 %)
Missing/ Unknown	57 (5.3 %)	6 (10.5 %)	99 (8.8 %)	387 (13.3 %)	117 (16.4 %)

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma.

Table 2
Univariable analysis of axillary surgery in patients with ypN0 status.

	Odds Ratio	95 % CI	p-value
Age of patient			
<40	1(ref)	–	–
40–54	0.66	0.53–0.81	<0.001
55–69	0.47	0.38–0.58	<0.001
70+	0.30	0.22–0.39	<0.001
Ethnicity			
White	1(ref)	–	–
Black	1.05	0.88–1.25	0.529
Other/Unknown	1.19	0.92–1.53	0.172
Histology			
IDC	1(ref)	–	–
ILC	0.17	0.11–0.28	<0.001
IDC + ILC	0.36	0.23–0.58	<0.001
Other	1.87	1.37–2.57	<0.001
Grade			
Well differentiated	1(ref)	–	–
Moderately differentiated	1.78	1.03–3.07	0.037
Poorly differentiated	5.15	3.03–8.74	<0.001
Missing/Unknown	2.27	1.29–3.99	0.004
Clinical T stage			
cT1	1(ref)	–	–
cT2	1.14	0.97–1.34	0.089
Pathologic T stage			
ypT0	17.79	14.50–21.82	<0.001
ypTIS	10.57	7.00–15.96	<0.001
ypT1	1(ref)	–	–
ypT2	0.22	0.16–0.29	<0.001
ypT3	0.15	0.06–0.39	<0.001
ypT4	0.25	0.06–1.04	0.058
Unknown	1.06	0.81–1.39	0.646
Receptor status			
HR-/HER2-	5.09	4.21–6.16	<0.001
HR+/HER2+	4.52	3.68–5.54	<0.001
HR-/HER2+	11.05	8.79–13.89	<0.001
HR+/HER2-	1(ref)	–	–
Missing/Unknown	1.11	0.82–1.51	0.478

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma.

compared to older patients (OR for 40–54 years: 0.76; CI 0.58–1.00; p-value = 0.05; OR for 55–69 years: 0.61, CI 0.47–0.81; p-value = 0.001; OR for 70+ years: 0.42, CI 0.29–0.60; p-value <0.001). Histological type, specifically IDC, retained statistical significance in predicting the likelihood of achieving ypN0 compared to ILC alone (OR 0.54; CI 0.31–0.94; p-value = 0.029). However, IDC with lobular features, along with tumor grade, did not remain significant. Clinical T2 tumors demonstrated a significant association with ypN0 response (OR 1.93; CI 1.57–2.38; p-value <0.001) despite showing no association on the univariable analysis. Achieving ypN0 was also significantly linked to patients having a pathologic stage of ypT0 or ypTis (OR 12.73; CI 10.25–15.81; p-value <0.001 and OR 8.73; CI 5.59–13.63; p-value <0.001 respectively).

Table 3
Multivariable analysis of axillary surgery in patients with ypN0 status.

	Odds Ratio	95 % CI	p-value
Age of patient			
<40	1(ref)	–	–
40–54	0.76	0.58–1.00	0.054
55–69	0.61	0.47–0.81	0.001
70+	0.42	0.29–0.60	<0.001
Histology			
IDC	1(ref)	–	–
ILC	0.54	0.31–0.94	0.029
IDC + ILC	0.63	0.35–1.15	0.136
Other	1.50	0.97–2.32	0.062
Grade			
Well differentiated	1(ref)	–	–
Moderately differentiated	0.82	0.44–1.55	0.560
Poorly differentiated	1.17	0.63–2.17	0.615
Missing/Unknown	0.75	0.37–1.50	0.421
Clinical T stage			
cT1	1(ref)	–	–
cT2	1.93	1.57–2.38	<0.001
Pathologic T stage			
ypT0	12.73	10.25–15.81	<0.001
ypTIS	8.73	5.59–13.63	<0.001
ypT1	1(ref)	–	–
ypT2	0.20	0.15–0.27	<0.001
ypT3	0.14	0.06–0.37	<0.001
ypT4	0.21	0.05–0.90	0.036
Unknown	2.15	1.47–3.16	<0.001
Receptor status			
HR-/HER2-	2.48	1.94–3.17	<0.001
HR+/HER2+	2.26	1.75–2.91	<0.001
HR-/HER2+	3.97	2.95–5.35	<0.001
HR+/HER2-	1(ref)	–	–
Missing/Unknown	0.62	0.38–0.99	0.049

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma.

Receptor status continued to display significant associations with nodal response, specifically, HR-/HER2+ (OR 3.97; CI 2.95–5.35, p-value <0.001), HR-/HER2- (OR 2.48; CI 1.94–3.17; p-value <0.001), and HR+/HER2+ (OR 2.26; CI 1.75–2.91; p-value <0.001) maintained a significant association with ypN0.

4. Discussion

Clinical trials have demonstrated the feasibility of selectively omitting ALND in patients with clinically node-positive breast cancer following NACT, specifically in those who exhibit a favorable treatment response. One benefit of this approach is to avoid exposing patients to the potential morbidity or complications of ALND, including lymphedema, shoulder dysfunction, nerve injury, or muscle paralysis,[3–6] particularly when there is a pathologic complete response. However, these trials have included patients classified predominantly as cN1.[12–14] The literature has not extensively reported on outcomes of axillary de-escalation in patients presenting with cN2 disease. This lack of data leaves uncertainty regarding the optimal surgical management for these patients.

In this large cohort analysis of cN2 breast cancer, the results demonstrated that 18.15 % of patients with cN2 disease down-staged to ypN0, suggesting that omission of ALND may be feasible in these select cases. Factors associated with axillary downstaging include pathologic breast tumor response (i.e., breast pCR), HER2+ or HR-/HER2-receptor status, younger age, and clinical T2 stage.

The observed association between pathologic breast tumor response, receptor status, and nodal response rates to neoadjuvant chemotherapy (NACT) aligns with previous research which has highlighted the importance of these factors in predicting nodal response.[20–22]

The association between younger age and axillary downstaging may reflect that younger, healthier patients with fewer co-morbidities are better able to tolerate and complete neoadjuvant chemotherapy (NACT), including more aggressive regimens, leading to greater treatment response. In addition, there may be inherent biologic differences in younger patients with breast cancer that afford improved response rates to systemic therapy. This observation resonates with studies that have found higher pCR rates in younger patients, although the underlying mechanisms remain an area of ongoing investigation.[23,24]

The observation that cT2 tumors more frequently achieve a ypN0 status compared to cT1 tumors may be attributed to the hypothesis that more aggressive tumor biology could lead to larger tumors at the time of treatment. These larger tumors may be associated with tumor profiles that are particularly responsive to chemotherapy, such as high-grade, triple-negative, or HER2-positive subtypes. Another hypothesis is that larger tumors (cT2) may have more genetic mutations and heterogeneity compared to smaller tumors (cT1). This increased genetic heterogeneity may provide more targets for chemotherapy, potentially improving the response rates of neoadjuvant therapy. Additional research may be warranted to further elucidate this finding. The cumulative findings of the current study are in concordance with previous research identifying similar factors that influence the likelihood of axillary downstaging. However, the current study's unique focus on patients with more advanced nodal involvement (cN2) provides valuable insight into a group previously underrepresented in the literature. These findings indicate that the majority of patients with cN2 breast cancer have residual axillary disease after NACT, warranting the use of ALND. This approach aligns with current guidelines, such as those from the National Comprehensive Cancer Network (NCCN) and remains generally applicable until further evidence from clinical trials is available.[25,26] The Alliance A011202 trial is a Phase III study comparing ALND to axillary radiation in patients with cT1-3 N1 breast cancer who have positive sentinel lymph nodes after NACT. The primary objective is to evaluate whether radiation to the undissected axilla and regional lymph nodes is not inferior to ALND plus regional lymph node radiation in terms of recurrence.

However, there exists a specific subset of patients with cN2 breast cancer who may achieve a pathologic complete response, potentially qualifying them for de-escalation of axillary surgery. This subset of patients can be characterized by specific clinicopathologic factors, underscoring the importance of careful patient selection if considering omission of ALND in this context.

There are inherent limitations to this study due to constraints associated with the retrospective database analysis. The database does not contain information on specific chemotherapy regimens or adherence to treatment. There is no information on the preoperative intent of axillary surgery, success rate of SLNB following NACT, initial pathology from the SLNB, or specific findings leading to ALND. Furthermore, information cannot be obtained regarding clinical or patient decision-making factors, which further restricts the ability to discern certain nuances when interpreting the findings. The study is also not able to assess the oncologic safety of de-escalation of axillary surgery. This is because the NCDB does not provide data on recurrence or breast cancer-specific survival. Consequently, while the results provide insights into the feasibility and immediate outcomes of different surgical approaches, it cannot offer long-term oncologic safety data. Despite these limitations, the use of the NCDB provided the necessary cohort size to overcome the constraints of previous clinical trials and provide valuable insight into the management of this patient population.

Risk stratifying patients with cN2 disease and leveraging factors such as receptor status and breast tumor response may help identify suitable candidates for potential de-escalation of axillary surgery. This approach could spare select patients from the associated morbidity and complications of ALND to better address quality of life needs. However, the long term oncologic outcomes remain uncertain.

Future research should focus on creating comprehensive analytic models to help accurately predict downstaging in patients with cN2 disease. Additionally, the long-term clinical outcomes associated with de-escalation strategies in these patients needs to be assessed. Further clinical trials and expanded registries could help assess the safety and

efficacy of omitting ALND in this particular patient group.

5. Conclusion

The majority of patients with cN2 breast cancer will have residual disease following NACT and subsequently require ALND. However, a distinct subset of patients, characterized by specific clinicopathologic features, may achieve downstaging to ypN0 and potentially be suitable candidates for axillary surgery de-escalation. These findings highlight the need for additional research to clarify and establish criteria for identifying patients who may benefit from omission of ALND. Such a strategy could reduce the risks and morbidity for selected patients. Further research is warranted to explore the long-term oncologic outcomes associated with this approach.

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Dr. James is a scientific consultant for Perimeter Medical.

Statements & declarations

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CRediT authorship contribution statement

Kathryn Capasso: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Samir Mitri:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation. **Estefania Roldan-Vasquez:** Writing – original draft, Visualization, Formal analysis, Conceptualization. **Rene Flores:** Writing – original draft, Visualization, Formal analysis, Conceptualization. **Shreya Bhasin:** Writing – original draft, Visualization, Data curation. **Giulia Borgonovo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Roger B. Davis:** Supervision, Software, Methodology, Formal analysis. **Ted James:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

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