Castleman's Disease: Systematic Analysis of 416 Patients from the Literature

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the centricity and histopathology profiles of each of the three classes of HIV-negative patients identified in this analysis.
2. Correlate nosological classification and outcomes in patients with Castleman's disease.

CME

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ABSTRACT

Background. Castleman's disease is a rare primary disease of the lymph nodes with limited available clinical information.

Methods. A systematic literature search identified 416 cases amenable to detailed analysis.

Results. In HIV⁺ patients, centricity, pathology type, the presence of symptoms, gender, and age all predict outcome in univariate analyses. The 3-year disease-free survival (DFS) rate for patients with unicentric hyaline vascular disease (49.5% of cases, class I) was 92.5%, versus 45.7% for those with multicentric plasma cell disease (20.2% of cases, class III) and 78.0% for those with any other combination (22.6% of cases, class II) ($p < .0001$).

HIV⁺ patients (class IV) exclusively presented with multicentric plasma cell disease and had a 3-year DFS rate of only 27.8%. Kaposi's sarcoma and lymphoma were observed in 59.3% and 9.4% of HIV⁺ patients and in 2.6% and 3.6% of HIV[−] patients ($p < .0001$). Paraneoplastic pemphigus and the syndrome of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes were observed exclusively in HIV[−] patients at a rate of 1.3% and 1.8%, respectively.

Conclusion. Clinical, pathological, and viral markers allow for the classification of Castleman's disease into groups with markedly different outcomes and disease associations. *The Oncologist* 2011;16:1316–1324

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INTRODUCTION

Castleman described the first patient with this rare primary lymph node disease in 1954 [1], followed by a series in 1956 [2]. A number of excellent reviews are available and give general oversight [3–9], focus on pathogenesis [4, 10], pathological features [11, 12], clinical presentation in HIV[−] [13] and HIV⁺ [14, 15] patients, and management aspects [8, 16, 17].

Most cases of Castleman's disease are reported in HIV[−] patients. Yet it is not quite clear what the prognosis of Castleman's disease in this group is and which factors allow outcome prediction. The early literature on Castleman's disease is based on a very limited number of cases and proposes classification based on centricity, that is, the presence of a single disease focus versus multiple disease foci [2, 11]. A more recent approach proposes classification predominantly based on histopathogenic type, that is, hyaline vascular (HV) versus plasma cell (PC) disease [12]. However, there is no empiric information on the overall frequency or impact of these or other factors such as age, gender, and viral status.

Major progress was made by understanding the role of human herpesvirus type 8 (HHV-8) infection [4], but there is a significant subset of patients with typical Castleman's disease and negative viral testing. Finally, there are rare associated conditions and a possible transformation of Castleman's disease into lymphoma, but no empiric knowledge about their predominant clinical setting.

The present detailed review of 416 patients is designed to help answer the above questions. Results inform a simple and outcome-relevant classification system.

MATERIALS AND METHODS

Literature Search Strategies

A systematic search was conducted of the published literature on Castleman's disease. The databases searched included MEDLINE, Cochrane Database of Systematic Reviews, and ISI Thompson Web of Knowledge using the search term "Castleman's Disease" in September 2009. Searches were conducted with language restriction; these included English, German, French, and Spanish articles only. Hand search of articles' bibliographies was also performed using the ISI Thompson Web of Knowledge citation report, and further articles were retrieved. The search identified 1,791 articles in English, French, Spanish, and German. Of the 1,791 citations identified through the initial electronic search and screened for possible inclusion, 488 articles were retained following title and abstract reviews, giving a total of 1,000 patients with Castleman's disease (556 patients from case reports, 444 patients from small case series). Of these, 237 articles were accepted for this re-

view, giving a total of 416 patients. Full available data were stored on the remaining 584 patients reported in 251 further articles.

Inclusion Criteria

Articles were selected for closer review if the abstract or key words contained the term Castleman's disease in the form of case reports, controlled or comparative studies, or small case series. This yielded 1,791 articles. In cases of duplicate publications of individual patients, only the most complete study was included. The inclusion criterion was unambiguous evidence of Castleman's disease in the form of a detailed histology description demonstrating HV, PC, or mixed variant disease [11], because all other associated clinical and laboratory findings were helpful but nonspecific. The case reports and case series included in this analysis are referenced in online supplemental Data 1. We excluded patients with isolated polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome who failed to meet the diagnosis of Castleman's disease (online supplemental Data 2).

Data Extraction and Synthesis

Data were extracted by one researcher and checked by another using standardized extraction tables developed a priori. Data on individual cases were pooled in a single contingency SPSS table (SPSS Inc., Chicago, IL). The study reports on data obtained in two different groups.

Analysis of association of clinical and other findings was performed in the core group of 416 patients for whom a complete dataset containing age, gender, centricity (unicentric [UC] versus multicentric [MC]), histopathologic type (HV versus PC), presence of symptoms, presence of associated diseases, and information on death or recurrence during any length of follow-up was available (Table 1). In addition, for all these patients, the HIV status could be ascertained. In patients with MC disease, we included only patients with explicitly reported HIV status (positive or negative). HIV status was negative in 101 MC disease patients and positive in 32 MC disease patients. We assumed a negative HIV status for all patients with UC disease. This is based on the observation that a positive HIV status is exclusively associated with MC disease [3, 18–20]. Independently from this literature statement, we assessed HIV status in relation to centricity in all 1,000 patients available from the initial literature research. The full group of 1,000 patients is not otherwise reported on here because only partial datasets are available with regard to many other criteria analyzed. In these 1,000 patients, HIV status was reported by the authors for 90 patients with UC disease and was negative in all cases. HIV status was reported for 318 patients

Table 1. Histopathological presentation in 416 patients

Factor	All HIV ⁻ (n = 384)				All HIV ⁺ (n = 32)		p-value
	HV	PC	Mixed	p-value	All HIV ⁻	All HIV ⁺	HIV ⁻ versus HIV ⁺
Centricity, UCD/MCD (%)	206/17 (92.4)	48/64 (42.9)	29/20 (59.2)	<.0001	283/101 (73.7)	0/32 (0)	<.0001
Gender, male/female (%)	89/134 (39.9)	64/48 (57.1)	26/23 (53.1)	.007	179/205 (46.6)	29/3 (90.6)	<.0001
Age (yrs), <37/>37 (%)	181/42 (81.2)	76/36 (67.9)	31/18 (63.3)	.004	288/96 (75.0)	27/5 (84.4)	<.01
Classical B-symptoms, yes/no (%)	167/56 (74.9)	104/8 (92.9)	41/8 (83.7)	<.0001	312/72 (81.3)	31/1 (96.9)	<.01
Kaposi's sarcoma, yes/no (%)	3/220 (1.3)	5/107 (4.5)	2/47 (4.1)	.19	10/374 (2.9)	19/13 (59.3)	<.0001
PNP, yes/no (%)	5/218 (2.2)	0/112 (0)	0/49 (0)	.16	5/379 (1.3)	0	NS
POEMS, yes/no (%)	3/220 (1.3)	2/110 (1.8)	2/47 (4.1)	.4	7/377 (1.8)	0	NS
Lymphoma, yes/no (%)	4/219 (1.8)	8/104 (7.1)	2/47 (4.1)	<.05	14/370 (3.6)	3/29 (9.4)	NS
Death, yes/no (%)	12/211 (5.4)	19/93 (17.0)	10/39 (20.4)	<.0001	41/343 (10.7)	14/18 (43.8)	.005

p-values were calculated based on cross-table analysis.
Abbreviations: HV, hyaline vascular; MCD, multicentric disease; PC, plasma cell; PNP, paraneoplastic pemphigus; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes; UCD, unicentric disease.

with MC disease and was positive in 175 patients. Correlation analysis demonstrated a strong correlation between centricity and HIV status (χ^2 , 86.7; $p < .0001$), and the factor UC disease had a 100% specificity for a negative HIV status in this group.

Outcome analyses using Kaplan–Meier statistics, receiver operating characteristic (ROC) statistics, and univariate analysis were performed in the subset of 166 patients (148 HIV⁻, 18 HIV⁺) for whom a complete dataset containing centricity (UC versus MC), histopathology type (HV versus PC), age, gender, presence of symptoms, and outcome at 3 years, defined as 3-year disease-free survival (DFS), was available. The 3-year DFS rate was defined as follows: an event was defined as either death resulting from disease or recurrence of disease. The observation interval was 3 years (36 months) or until death or recurrence. Because all patients with shorter observation intervals and those who died as a result of other diseases prior to 3 years after their initial diagnosis were excluded from the analysis, there are no censored patients. Results are found in Tables 2 and 3.

Case reports contained highly variable information regarding symptoms. We recorded all symptoms in the initial extraction table. We then classified a patient as having Castleman-related B-symptoms if the authors reported at

Table 2. Centricity, histopathology type, gender, age, and presence of symptoms influence the 3-year disease-free survival probability in a univariate analysis of 148 HIV⁻ patients

Factor	Univariate	
	Odds ratio (95% CI)	Sign ^a
Centricity (MCD)	8.2 (3.4–19.4)	<.0001
Histopathology type (PC)	6.7 (2.7–16.3)	<.0001
Gender (male)	3.1 (1.4–7.1)	.005
Age (>37 years)	6.4 (2.4–16.6)	<.0001
Symptoms (present)	2.1 (0.9–5.0)	.08

^aSign: p-values of the coefficients or the probability.
Abbreviations: CI, confidence interval; MCD, multicentric disease; PC, plasma cell.

least one of the following: fever, fatigue, weight loss, or night sweats.

HHV-8 status was not reported in many cases; therefore data on HHV-8 were excluded.

Values for the median, 95% confidence interval (CI), χ^2 test results, univariate statistics, ROC statistics, and Kaplan–Meier statistics were calculated using SPSS software

Table 3. Nosological classification of Castleman's disease, associated conditions, and outcome

Class (entity)	n of patients n (%)	n = 416					Associated conditions n = 416				n = 166	n = 416
		Centricity, UCD %	HV, %	Gender, male %	Systemic symptoms, %	Age, <37 yrs	KS, %	PNP, %	POEMS, %	Lymphoma, %	3-yr DFS (n = 166)	Overall outcome: variable follow-up intervals (n = 416)
I (UCD-HV)	206 (49.5)	100	100.0	39.8	75.2	64.6	0.5	2.4	0.5	1.0	92.5 ^{aII, bIII, bIV}	96.1 ^{aII, bIII, bIV}
II (other)	94 (22.6)	81.9	18.1	51.1	88.3	50.0	2.1	0	3.2	4.3	78.8 ^{aI, aIII, aIV}	89.4 ^{aI, aIII, bIV}
III (MCD-PC)	84 (20.2)	0	0	65.5	88.1	23.8	8.3	0	3.6	9.5	45.7 ^{bI, aII, n.s.IV}	72.6 ^{bI, aII, n.s.IV}
IV (HIV ⁺)	32(7.7)	0	18.5	90.6	96.9	34.4	59.3	0	0	9.4	27.8 ^{bI, aII, n.s.III}	56.3 ^{bI, bII, n.s.III}
Overall I–III	384 (92.3)	73.7	58.1	46.6	81.2	52.1	2.6	1.3	1.8	3.6	78.4	89.3
Overall I–IV	416 (100.0)	68.0	53.6	50.0	82.5	50.7	7.0	1.2	1.7	4.1	72.9	86.7
Difference by class	Sign.	Sign.	Sign.	Sign.	Sign.	Sign.	Sign.	n.s.	n.s.	Sign.	Sign.	Sign.

Superscript letters indicate a significant difference—^a $p < 0.01$ or < 0.001 ; ^b $p < 0.0001$; ^{n.s.} not significant—compared with the other classes. For example, 90%^{aII, bIII, bIV, bV} indicates a significant difference in outcome between this class and class II at $p < .01$ and classes III and IV each at $p < .0001$.

Abbreviations: DFS, disease-free survival; HV, hyaline vascular; KS, Kaposi's sarcoma; MCD, multicentric disease; PC, plasma cell; PNP, paraneoplastic pemphigus; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; UCD, unicentric disease.

version 16.0 (SPSS Inc., Chicago, IL). Significance levels are two-sided throughout the manuscript.

RESULTS

In the cohort of 384 HIV[−] patients, similar numbers of cases were reported with HV and PC presentation, and for both genders (Table 1). More patients had UC disease and most suffered symptoms. Castleman's disease was reported in all age groups, but with obvious differentiation according to gender, centricity, and histopathology type (Fig. 1). The presentation of Castleman's disease in HIV⁺ patients ($n = 32$) was significantly different from its presentation in the overall group or the group of all HIV[−] patients (Table 1).

Association of Clinical and Pathological Findings

Correlation analysis in the cohort of 384 HIV[−] patients revealed strong and significant associations between the analyzed factors. Pearson χ^2 correlation coefficients were as follows: centricity–histopathology, 95.7; $p < .0001$ (UC HV and MC PC disease); centricity–gender, 12.0; $p < .0001$ (UC disease–female and UC disease–male); centricity–age, 44.0; $p < .0001$ (UC disease–age <37 years and UC disease–age >37 years); histopathology–gender, 9.6; $p < .0001$ (HV–female and PC–male); histopathology–age, 18.6; $p < .0001$ (HV–age < 37 years and PC–age >37 years); and gender–age, 8.5; $p < .0001$ (female–age <37 years and male–age >37 years). Symptoms did not correlate significantly with any variable except histopathology (χ^2 , 14.1; $p < .0001$). The by far strongest correlation was observed between centricity and histopathology (online supplemental Table 1).

Outcome Predictors in HIV[−] Patients

All examined factors were significant outcome predictors on univariate or Kaplan–Meier analysis in the group of 166 patients with known HIV status (148 HIV[−]; 18 HIV⁺) and information on 3-year DFS (Table 2 and Fig. 2). In the group of 166 patients with known HIV status, recurrence was observed in four of 80 (5.0%) class I patients, three of 35 (8.6%) class II patients, three of 33 (8.6%) class III patients, and one of 18 (5.6%) class IV patients, whereas death resulting from the disease occurred in two of 80 (2.5%) class I patients, four of 35 (11.4%) class II patients, 15 of 33 (45.4%) class III patients, and 12 of 18 (66.7%) class IV patients ($p < .0001$) (Fig. 3). Given the above intercorrelation of all tested predictors, the data are not amenable to regression hypothesis testing.

Predominant Disease Presentations (Classes)

Based on this intercorrelation and evidence of numerically predominant clusters (Table 3), we identified three predominant phenotypes of Castleman's disease in HIV[−] patients: (a) class I, UC HV disease; (b) class II, UC PC or mixed pathology disease or MC HV disease; and (c) class III, MC PC disease. Class IV includes only HIV⁺ patients, who exclusively present with multicentric plasma cell disease.

ROC analysis of the classification model was performed with regard to outcome (3-year DFS), rather than an approach based on either factor alone. Using the proposed classification scheme results in a good model with an area under the curve (AUC) of 0.81 (95% CI, 0.74–0.89; $p < .0001$) (online supplemental Fig. 1), as opposed to lower AUCs for either factor alone (online supplemental Table 2).

Figure 1. Age distribution in 384 HIV⁻ patients. (A): Grouped by decade: overall median age, 37 years. (B): Grouped by centricity: UCD median age, 30 years; MCD median age, 52 years. (C): Grouped by gender: female median age, 33 years; male median age, 38 years. (D): Grouped by histopathology type: HV median age, 30 years; PC median age, 41 years.

Abbreviations: HV, hyaline vascular; MCD, multicentric disease; PC, plasma cell; UCD, unicentric disease.

We confirmed the fundamental observation that class I and class III disease are the predominant nosological entities using analysis of a larger cohort of 931 patients with Castleman's disease for whom histopathology and centricity were known. Of these 931 patients, 326 (35.0%) fell into class I, 185 were in class II (19.9%), 252 (27.1%) were in class III, and 168 (18.0%) were in class IV. Within this larger cohort, a Pearson χ^2 test confirmed the strong correlation between centricity and histopathology (with a coefficient of 302; $p < .0001$) already identified in the group of 416 patients with known HIV status.

Outcome Analysis Based on Classification

The 3-year DFS rate varied strongly among these groups, at 92.5% for class I patients, 78.8% for class II patients, and 45.7% for patients with MC PC disease ($p < .0001$) (Fig. 3 and Table 3). HIV⁺ patients (class IV) exclu-

sively presented with MC PC disease and had a 3-year DFS probability of only 27.8% (Fig. 3 and Table 3). Results of application of the above classification system were validated in the complete group of 384 patients with variable follow-up intervals (Table 2) (also see online supplemental Fig. 2 for Kaplan–Meier statistics and online supplemental Fig. 3 and online supplemental Table 3 for ROC statistics).

Disease Associations

Associated diseases were observed in numerous patients (Table 1). Paraneoplastic pemphigus (PNP) and POEMS were restricted to HIV⁻ patients. Lymphoma and Kaposi's sarcoma were observed in both groups, but with significantly greater numbers in the HIV⁺ group (relative risk, 4.5 and 13.5, respectively; $p < .0001$).

Figure 2. Centricity, histopathology type, gender, and age influence the 3-year disease-free survival rate in a Kaplan–Meier analysis of 148 HIV⁺ patients.

Abbreviations: HV, hyaline vascular; MCD, multicentric disease; PC, plasma cell; UCD, unicentric disease.

DISCUSSION

Despite its rarity, Castleman's disease has recently sparked major research interest because of its association with HHV-8 and HIV infection, providing a model of initially benign viral disease with cytokine-driven propagation into expanding infected cell pools and malignant transformation [4, 5, 10]. In HIV⁺ patients, there is excellent information on the clinical and laboratory presentation from a few, but highly informative, studies on large cohorts [3, 5, 21, 22]. In HIV[−] patients, information is dispersed in case reports and small case series, and clinical experience is diluted by multiple diagnostic and treatment pathways. It, hence, seems unlikely that any single-center experience will contribute the needed information for HIV[−] patients in the near future.

Our results provide the first broad-based empiric information on the presentation of Castleman's disease in HIV[−]

patients. They substantiate former suggestions based on smaller cohorts [11, 23, 24], highlighting the importance of pathological presentation. They identify centricity and histopathology type as close correlates and establish their near equal outcome relevance. Based on empiric clinical observations and established pathogenic theory, we identified nosological subgroups in Castleman's disease. The resulting novel classification system provides a valuable model for prediction of midterm outcome.

Table 1 establishes the patterns of clinical and histopathological presentation of Castleman's disease in a cohort of 384 patients. Analysis corroborated the impression that HIV-related Castleman's disease is an altogether distinct clinical manifestation because there are highly significant differences between HIV⁺ and HIV[−] patients for every single factor included in the analysis. Beyond this,

Figure 3. Variation in the 3-year disease-free survival rate in a Kaplan–Meier analysis of 166 patients depending on nosological classification. **(A):** Only HIV[−] patients were included ($n = 148$). Class I, HV UCD; class II, PC UCD or mixed pathology UCD or HV MCD; class III, PC MCD. **(B):** Additionally includes HIV⁺ patients ($n = 166$).

Abbreviations: HV, hyaline vascular; MCD, multicentric disease; PC, plasma cell; UCD, unicentric disease.

there are strong associations between most factors, notably between centricity and histopathological type. There is a spectrum of variations within each potential classifier proposed in previous literature. For example, histological type ranges from pure HV disease to pure PC disease, with varying degrees of mixed features in-between. Centricity ranges from pure UC disease, that is, a single center of disease, to UC disease with several foci [25], to MC disease with an anatomical area of predominance, and to truly MC disease [25].

The age distribution is distinctly different, with presentation in the early decades of life in female patients, UC disease, and HV disease, compared with presentation in the second half of life in male and MC patients (Fig. 1). In the context of a suspected infectious etiology of Castleman's disease, this points to a different agent, mode of transmission, or age-related susceptibility factor in these cohorts.

The clinical presentation in HIV[−] patients is dominated by two main nosological entities, that is, UC HV disease and MC PC disease, which accounts for 69.7% of all cases. There is a numerically smaller group of patients sharing various transitions between these on the levels of histopathology and centricity (Table 3). Females predominantly suffer from UC and HV disease (Tables 1 and 3). We demonstrate that there is a strong correlation between histopathology type and centricity and other key clinical factors including gender, age, and symptoms. This complexity is acknowledged, but needs to be effectively reduced in order to obtain clinically useful information that could be used to indicate treatment needs, expected time course of the disease, and midterm outcome. For clinical use, there is a need

for a classification system that accounts for the discontinuous spectrum of Castleman's disease rather than relying on the predictive value of any isolated presenting feature.

Given the correlations among these factors, the relative impact of the factors, for example, on outcome, cannot be assessed by regression analysis. We have, hence, grouped patients based on the strongest correlation identified, that is, the correlation between centricity and histopathogenic type. This approach is additionally supported by the fact that these factors had the highest odds ratios for adverse outcome on univariate analysis (Table 2). It also conforms to the views of the majority of the previous authors who considered these factors to be paramount in the assessment of Castleman's disease [11–13, 26]. Based on centricity and histopathology type, three distinct classes of HIV[−] patient can be identified, who differ significantly with regard to gender, age distribution, and symptom frequency (Table 3). These cohorts also differ significantly with regard to their 3-year DFS rates (Fig. 3). HIV⁺ patients were considered a class of their own for reasons outlined above.

Ultimately, outcome prediction is the most important information expected from nosological subgroups, because this best informs the patient's outlook on his disease as well as the urgency and scope of physicians' actions. Kaplan–Meier analysis demonstrated that outcome varied significantly among the defined classes (Fig. 3). We used the outcome 3-year DFS as a surrogate parameter of overall disease-free survival because this allowed analysis of a reasonably sized cohort of 166 patients and because the event death or recurrence had occurred in >50% of patients in class III and class IV at this point. Analysis using overall

outcome, including censored patients and follow-up data up to 20 years, yielded very similar results, confirming the validity of the results obtained in the smaller cohort ($n = 166$) using analysis of the larger cohort of 416 patients (online supplemental Fig. 2). Although the Kaplan–Meier analysis provided insight into the relevance of factors to outcome, it does not assess the quality of the employed model. We used the 3-year DFS rate as an endpoint to assess the model produced on the basis of centricity, histopathology, and HIV status through ROC statistics. The AUC was measured as 0.81 ($p < .0001$) (online supplemental Fig. 1), a finding generally considered to indicate good model fit. Use of this classification system was superior to use of either factor alone (online supplemental Table 2). In our view, this novel empiric evidence corroborates former approaches to classification based both on centricity [7, 11, 26] and on histopathogenic type [11, 12, 27, 28], and unifies them into combined classes. The classification is based on straightforward clinical and pathological information and could aid in providing physicians and patients with a realistic prognostic outlook.

The rare conditions associated with Castleman's disease are clearly restricted to specific subgroups. Possible causes of such associations are outlined in a number of reviews [6, 10, 12, 29] and reports relating to the specific entities, that is, Kaposi's sarcoma [9, 30], PNP [31], POEMS [29], and lymphoma [30, 32–35].

Based on this analysis, a number of summarizing statements can be made.

First, centricity and histopathogenic type are the domi-

nating clinical classifiers in HIV[−] patients. They are closely interlinked and inform an outcome-relevant classification of good model quality.

Second, classification is significantly enhanced by including information related to viral infection, that is, HIV status.

Finally, Kaposi's sarcoma prevails in HIV⁺ patients, but can be found in a significant subgroup of class III patients. Lymphoma is a threatening complication in patients with class II–IV disease. PNP is exclusively observed in class I disease.

With all its limitations, the value of the current analysis is the establishment of a large number of factual statements replacing former indications of trends or beliefs in a disease in which most authors have seen or reported only single patients or a very limited number of patients. Its obvious limitations relate to limited follow-up intervals, a retrospective approach, and missing information on essential features such as the HHV-8 status of many patients. Results need to be interpreted with these caveats in mind. It is crucial to overcome the above deficits and we most strongly advocate the creation of a worldwide, possibly Web-based, database prospectively retaining case information.

AUTHOR CONTRIBUTIONS

Conception/Design: Klaus-Martin Schulte

Provision of study material or patients: Klaus-Martin Schulte

Collection and/or assembly of data: Klaus-Martin Schulte, Nadia Talat

Data analysis and interpretation: Klaus-Martin Schulte, Nadia Talat

Manuscript writing: Klaus-Martin Schulte

Final approval of manuscript: Klaus-Martin Schulte, Nadia Talat

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"Healing" by Janna, a cancer patient, United States