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Longitudinal Changes in Salivary Secretory Immunoglobulin A, Interleukin-6, and Interleukin-8 During the First Year Following Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract

Objectives

To investigate longitudinal changes in salivary secretory immunoglobulin A (sIgA), interleukin-6 (IL-6), and interleukin-8 (IL-8) during the first year after allogeneic hematopoietic stem cell transplantation (allo-HSCT), and their associations with serum biomarkers and oral graft-versus-host disease (GvHD).

Materials and Methods

In this prospective observational study, 35 patients contributed 76 saliva sample-visits before transplantation and approximately 100, 200, and 365 days thereafter. Salivary biomarkers were quantified by ELISA and analyzed using generalized estimating equations accounting for repeated measurements.

Results

Significant longitudinal changes were observed for sIgA and IL-8 (both $p < 0.001$), remaining significant in sensitivity analyses. IL-6 showed a time effect in the primary analysis ($p = 0.011$), but not after exclusion of zero-coded observations ($p = 0.600$). No significant associations were observed between salivary biomarkers and their corresponding serum concentrations. Higher oral GvHD activity was associated with lower salivary sIgA (ratio 0.29; 95% CI 0.12–0.70; $p = 0.006$), but not with IL-6 or IL-8.

Conclusions

Salivary sIgA and IL-8 exhibited distinct longitudinal changes after allo-HSCT. Lower sIgA concentrations were associated with greater oral GvHD activity.

Clinical Relevance:

Salivary sIgA may offer a non-invasive approach to investigating oral GvHD involvement, although its clinical utility requires validation in larger prospective studies.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for malignant and non-malignant hematologic diseases, enabling the replacement of a dysfunctional hematopoietic system with donor-derived stem cells [1]. Despite its therapeutic efficacy, allo-HSCT is associated with substantial morbidity due to complications such as infections, relapse, and graft-versus-

host disease (GvHD), which remains a major cause of post-transplant morbidity and mortality [1]. GvHD results from donor-derived immune cells recognizing host tissues as foreign, initiating a complex inflammatory cascade driven by cytokine release and immune cell activation [2, 3]. The oral cavity is one of the most frequently affected sites, particularly in chronic GvHD, presenting with erythema, lichenoid lesions, ulcerations, xerostomia, and functional impairment [4, 5].

Diagnosis and monitoring of GvHD rely largely on clinical assessment and, in some cases, invasive biopsy procedures. Therefore, there is increasing interest in identifying reliable biomarkers that allow early detection, risk stratification, and monitoring of disease progression after allo-HSCT [6, 7]. Blood-based biomarkers, including cytokines, microRNAs, and cellular markers, have been extensively studied in this context [8–13]. Among inflammatory mediators, interleukin-6 (IL-6) and interleukin-8 (IL-8) are of particular relevance. IL-6 is a pleiotropic cytokine involved in immune regulation, acute-phase responses, and T-cell differentiation, and has been implicated in the pathogenesis of GvHD as well as tumor progression [14–20]. Elevated IL-6 levels in blood have been associated with the occurrence of GvHD [21–23]. IL-8, a pro-inflammatory chemokine, plays a key role in neutrophil recruitment and angiogenesis and has been linked to tumor progression, leukemia biology, and adverse outcomes after allo-HSCT [24–28].

Secretory immunoglobulin A (sIgA) represents an essential component of mucosal immunity. As the predominant immunoglobulin in body secretions, sIgA contributes to pathogen neutralization and maintenance of mucosal homeostasis [29]. Several studies have reported altered, frequently reduced, salivary sIgA concentrations following hematopoietic stem cell transplantation [30–32], with further evidence suggesting an association between reduced sIgA levels and the presence or severity of GvHD [30, 33, 34].

Saliva has emerged as a promising diagnostic fluid because its collection is non-invasive, cost-effective, and readily repeatable, making it particularly suitable for longitudinal monitoring in vulnerable patient populations [35]. It contains biologically relevant molecules derived from local tissues and the systemic circulation and may therefore reflect local and systemic processes [36, 37]. Salivary diagnostics has been investigated in endocrine disorders, oral diseases, cancer, and autoimmune disease [37–40]. Similarities between chronic GvHD and autoimmune diseases such as Sjögren's syndrome further support investigation of salivary biomarkers, as altered cytokine and sIgA concentrations have been described in these conditions [4, 38]. Nevertheless, salivary biomarker data after allo-HSCT remain scarce.

Previous studies evaluating salivary inflammatory cytokines in HSCT populations have largely addressed treatment-related oral complications, including oral mucositis, or cross-sectional associations with oral chronic GvHD [41–44], rather than longitudinal biomarker trajectories over the first post-transplant year.

The primary objective of this study was therefore to evaluate longitudinal changes in salivary sIgA, IL-6, and IL-8 during the first year following allo-HSCT. Secondary objectives were to assess whether salivary concentrations were associated with the corresponding serum biomarkers while accounting for repeated

measurements within patients, and to evaluate associations between salivary biomarkers and oral GvHD severity after transplantation. These analyses were exploratory and were intended to characterize biomarker trajectories and associations rather than to establish diagnostic or prognostic cut-offs.

Materials and Methods

Study Design and Patient Cohort

This prospective longitudinal observational study included adult patients undergoing allo-HSCT at the University Medical Center Mainz, Germany (Table 1). Clinical examinations and biospecimen collection were scheduled before transplantation (T1) and 100 (T2), 200 (T3), and 365 days (T4) after allo-HSCT. The study was approved by the local ethics committee (873.205.06(5303)).

The biomarker-analysis cohort comprised 35 patients who contributed at least one evaluable salivary biomarker measurement at one or more of the four study visits. A total of 76 saliva sample-visits were available: 30 at T1, 15 at T2, 19 at T3, and 12 at T4. Not every patient contributed a sample at every study visit; consequently, individual patients contributed measurements at between one and four of the scheduled time points. Patients without a T1 sample could therefore contribute measurements at subsequent visits (supplementary table S1). Biomarker-specific availability differed because not every collected sample yielded a result for every analyte. The primary longitudinal models therefore included 74 sIgA observations from 35 patients, 73 salivary IL-6 observations from 34 patients, and 74 salivary IL-8 observations from 34 patients (supplementary table S1).

Table 1
Baseline characteristics of the patient cohort (*n = 35*).

Characteristic	Value
Age, years, mean ± SD (range)	55.5 ± 13.7 (27–73)
Sex, *n* (%)	
Male	22 (62.9)
Female	13 (37.1)
Underlying diagnosis, *n* (%)	
Acute myeloid leukemia	22 (62.9)
Acute lymphoblastic leukemia	3 (8.6)
Myelodysplastic syndrome	2 (5.7%)
Chronic myeloid leukemia	2 (5.7%)
Osteomyelofibrosis	2 (5.7%)
Follicular lymphoma	1 (2.9%)
Mantle-cell lymphoma	1 (2.9%)
Chronic myelomonocytic leukemia	1 (2.9%)
Other	1 (2.9%)
Total	35 (100.0%)

Oral GvHD Assessment

Oral mucosal involvement was assessed using the NIH Mouth cGVHD Activity Assessment Score (NIH oral cGVHD activity score). Because all patients had a score of 0 before transplantation (T1), inferential analyses of associations between oral GvHD severity and salivary biomarkers were restricted to T2–T4.

Saliva Collection and Processing

Unstimulated whole saliva was collected for 5 min by passive drainage into a graduated collection tube. Patients were instructed to refrain from eating and chewing gum for 90 min before sampling. Whenever feasible, collection was performed in a quiet, slightly dimmed environment between 09:00 and 12:00 to reduce potential circadian and environmental influences. Samples were kept chilled following collection and stored at − 20°C until biomarker analysis. Biomarker measurements were performed after several months of frozen storage.

Serum Biomarker Assessment

Peripheral blood samples were obtained at the four scheduled study time points. Serum concentrations of IgA, IL-6, and IL-8 were analyzed by the Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center Mainz. For serum–saliva association analyses, only matched serum–saliva pairs obtained from the same patient at the same study visit were included. Reference ranges were IgA 0.63–5.81 g/L, IL-6 < 27 pg/mL, and IL-8 < 62 pg/mL.

Salivary Biomarker Analysis

Frozen saliva samples were thawed and centrifuged at 3000 rpm for 15 minutes. Salivary sIgA was measured using the IgA Saliva ELISA (LDN, catalog no. SA E-6800; analytical range 0.5–400 µg/mL). IL-6 and IL-8 were determined using the Human IL-6 DuoSet ELISA (R&D Systems, catalog no. DY206-05; analytical range 9.4–600 pg/mL) and Human IL-8 DuoSet ELISA (R&D Systems, catalog no. DY208-05; analytical range 31.2–2,000 pg/mL), respectively. Saliva samples were diluted 1:3000 or 1:2000 for sIgA, analyzed undiluted for IL-6, and initially diluted 1:3 for IL-8, with subsequent measurements performed undiluted after protocol adjustment. Absorbance was measured at 450 nm with a reference wavelength of 620 nm using a SpectraMax iD5 microplate reader (Molecular Devices). Each sample was analyzed in triplicate, and the mean concentration was calculated using SoftMax Pro version 7 (Molecular Devices, San Jose, CA, USA).

Measurements outside the analytical range were repeated after adjustment of sample dilution. Measurements that remained below the lower analytical range after repeat analysis were assigned a value of 0 for statistical analysis.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (Version 29.0.2.0 (20), IBM Corp., Armonk, NY, USA). Biomarker concentrations were summarized at each visit as n, median, and interquartile range (IQR). No missing values were imputed.

To retain zero-coded observations, a biomarker-specific offset equal to one-half of the smallest non-zero concentration was added to all values before natural-log transformation. All inferential analyses used biomarker-specific linear generalized estimating equation (GEE) models on this scale, with a Gaussian distribution, identity link, exchangeable working correlation structure, and robust sandwich standard errors. Visit was modeled as a categorical factor.

The primary longitudinal models assessed changes in salivary sIgA, IL-6, and IL-8 across T1–T4 using Wald chi-square tests. The six within-biomarker pairwise visit contrasts were adjusted using the Holm method. Robustness was assessed by refitting these models after exclusion of zero-coded observations.

For serum–saliva associations, separate models paired serum IgA with salivary sIgA and serum IL-6 and IL-8 with their salivary counterparts. Each model included the corresponding log-transformed serum biomarker and visit. Serum effects were expressed as ratios of expected salivary concentrations associated with a two-fold higher serum concentration [exp (β × ln 2)].

Oral cGVHD analyses were restricted to T2–T4 because all baseline activity scores were zero since this cinical examination occurred before allo-HSCT. The models included oral cGVHD activity score and visit, with effects expressed as ratios of expected salivary concentrations per one-point higher activity score.

All tests were two-sided. Holm adjustment was limited to the within-biomarker pairwise time comparisons; no further multiplicity correction was applied because cross-biomarker and association analyses were exploratory. Effect estimates are presented with 95% confidence intervals (CI) alongside p values.

Results

Longitudinal Changes in Salivary Biomarkers

For sIgA, the numbers of available observations at T1 – T4 were 30, 14, 19, and 11, respectively. Median (IQR) concentrations were 0.003 (0.001–0.068) g/L at T1, 0.006 (0.0007–0.042) g/L at T2, 0.016 (0.001–0.127) g/L at T3, and 0.072 (0.057–0.203) g/L at T4. The overall effect of study time was statistically significant (Wald $\chi^2(3) = 20.30$, $p < 0.001$; 74 observations from 35 patients). After Holm adjustment, sIgA concentrations were higher at T4 than at T1 (ratio 8.93, adjusted $p < 0.001$), T2 (ratio 24.98, adjusted $p < 0.001$), and T3 (ratio 7.29, adjusted $p = 0.030$). The remaining pairwise contrasts were not statistically significant.

For salivary IL-6, the numbers of available observations at T1 – T4 were 29, 14, 19, and 11. Median (IQR) concentrations were 6.039 (4.433–8.621) pg/mL at T1, 5.760 (3.246–29.871) pg/mL at T2, 4.394 (1.110–7.842) pg/mL at T3, and 0 (0–0.634) pg/mL at T4. The primary GEE model showed an overall time effect (Wald $\chi^2(3) = 11.21$, $p = 0.011$; 73 observations from 34 patients). After Holm adjustment, T4 concentrations were lower than T1 (ratio 0.215, adjusted $p = 0.007$), T2 (ratio 0.132, adjusted $p = 0.034$), and T3 (ratio 0.394, adjusted $p = 0.037$). The remaining pairwise contrasts were not statistically significant.

For salivary IL-8, the numbers of available observations at T1 – T4 were 29, 15, 19, and 11. Median (IQR) concentrations were 166.352 (35.208–549.598) pg/mL at T1, 465.048 (162.970–616.124) pg/mL at T2, 435.552 (217.644–1226.409) pg/mL at T3, and 600.290 (322.479–1646.571) pg/mL at T4. The overall effect of study time was statistically significant (Wald χ^2 (3) = 16.44, $p < 0.001$; 74 observations from 34 patients). After Holm adjustment, the T1 – T3 contrast remained statistically significant, with higher IL-8 at T3 than at T1 (ratio 4.21, adjusted $p < 0.001$). None of the other five pairwise contrasts was statistically significant after Holm adjustment (Table 2, Fig. 1).

In sensitivity analyses excluding observations assigned a value of 0, the overall time effects remained significant for sIgA (Wald χ^2 (3) = 20.59, p < 0.001) and IL-8 (Wald $\chi^2(3)$ = 14.56, p = 0.002), whereas the time effect for IL-6 was no longer significant (Wald $\chi^2(3)$ = 1.87, p = 0.600; supplementary table S2).

Table 2
Salivary biomarker concentrations across the four study time points.

Biomarker	Time	n	Median (IQR)
sIgA (g/L)	T1	30	0.003 (0.001 — 0.0681)
	T2	14	0.006 (0.0007 — 0.042)
	T3	19	0.016 (0.001 — 0.127)
	T4	11	0.072 (0.057 — 0.202)
Salivary IL-6 (pg/mL)	T1	29	6.039 (4.433 — 8.621)
	T2	14	5.76 (3.246 — 29.871)
	T3	19	4.394 (1.11 — 7.842)
	T4	11	0 (0 — 0.634)
Salivary IL-8 (pg/mL)	T1	29	166.352 (35.208 — 549.598)
	T2	15	465.048 (162.969 — 616.124)
	T3	19	435.552 (217.644 — 1226.41)
	T4	11	600.29 (322.478 — 1646.57)

Association Between Salivary and Serum Biomarkers

After accounting for repeated measurements within patients and study time, no evidence of an association was observed between serum IgA and salivary sIgA. The estimated multiplicative change in salivary sIgA per doubling of serum IgA was 0.95 (95% CI 0.53–1.69; p = 0.855), based on 68 paired observations from 33 patients.

No evidence of an association between serum and salivary IL-6 was observed after accounting for repeated measurements within patients and study time. The multiplicative change in salivary IL-6 per doubling of serum IL-6 was 1.00 (95% CI 0.67–1.51; p = 0.983), based on 63 paired observations from 32 patients.

Similarly, no evidence of an association between serum and salivary IL-8 was observed after accounting for repeated measurements within patients and study time.

The multiplicative change in salivary IL-8 per doubling of serum IL-8 was 1.04 (95% CI 0.68–1.61; p = 0.853), based on 61 paired observations from 32 patients.

Association Between Salivary Biomarkers and Oral GvHD

Analyses of oral GvHD were restricted to post-transplant visits T2 – T4 and adjusted for study time. Higher NIH oral cGVHD activity scores were associated with lower salivary sIgA concentrations. Each 1-point higher NIH oral cGVHD activity score was associated with a multiplicative sIgA ratio of 0.29 (95% CI 0.12–0.70; p = 0.006), based on 37 observations from 21 patients.

No statistically significant association was observed between the NIH oral cGVHD activity score and salivary IL-6 (ratio per 1-point higher score 0.70, 95% CI 0.40–1.23; p = 0.211; 36 observations from 21 patients) or salivary IL-8 (ratio 0.90, 95% CI 0.67–1.21; p = 0.468; 37 observations from 21 patients; Table 3).

Table 3
Association between salivary biomarkers and oral GvHD severity.

Salivary biomarker	Observations, n	Patients, n	Ratio per 1-point higher NIH oral cGVHD activity score	95% CI	p
sIgA	37	21	0.29	0.12–0.70	0.006
IL-6	36	21	0.70	0.40–1.23	0.211
IL-8	37	21	0.90	0.67–1.21	0.468

Values are derived from time-adjusted generalized estimating equation models accounting for repeated observations within patients. Analyses were restricted to T2 – T4 because all NIH oral cGVHD activity scores were 0 at baseline. Ratios represent the multiplicative change in salivary biomarker concentration associated with a 1-point higher NIH oral cGVHD activity score. CI, confidence interval; GEE, generalized estimating equation.

Discussion

In this longitudinal cohort of 35 patients undergoing allo-HSCT, salivary sIgA and IL-8 changed significantly during the first post-transplant year. The time effect for sIgA and IL-8 remained present in sensitivity analyses, whereas the time effect for IL-6 was not robust after exclusion of zero-coded observations. Salivary sIgA, IL-6, and IL-8 were not associated with their corresponding serum concentrations after accounting for study time and repeated measurements within patients. In contrast, higher post-transplant oral cGVHD activity was associated with lower salivary sIgA. No corresponding association was observed for salivary IL-6 or IL-8.

Restricting the cohort to patients undergoing allo-HSCT provided a clinically homogeneous transplant setting. However, the number of available biomarker measurements decreased over time and differed

between biomarkers, particularly at T4. Consequently, estimates at later visits are less precise. In addition, biomarker concentrations may be influenced by collection and processing procedures [45–49].

In this study, unstimulated whole saliva was collected by passive drainage under predefined conditions and stored at − 20°C until analysis. As biomarker measurements were performed after several months of frozen storage, possible storage-related effects on analyte stability cannot be excluded when comparing these findings with studies using different pre-analytical protocols.

Salivary sIgA increased over time, with significantly higher concentrations at T4 than at T1, T2, and T3. Previous studies have described an early reduction in salivary sIgA after HSCT and, in some cohorts, subsequent recovery [30, 32]. Our data neither demonstrate nor exclude a similar early decrease, because the first post-transplant assessment was performed at approximately day 100. The higher sIgA concentrations at T4 are therefore an observation at the end of follow-up and should not be interpreted as proof of recovery from an unmeasured early decline.

Salivary IL-6 concentrations were lower at T4 than at the earlier visits in the primary analysis. However, this overall time effect was no longer present after exclusion of observations assigned a value of 0. The IL-6 result therefore depends on values at the lower analytical range and should be interpreted cautiously. In addition, only 11 IL-6 observations were available at T4. No association between salivary IL-6 and oral cGVHD activity was identified in the post-transplant analysis.

Salivary IL-8 also changed over time. After correction for all six pairwise comparisons, IL-8 concentrations were significantly higher at T3 than at T1; no other pairwise time-point difference remained statistically significant. Thus, the data support a difference between baseline and approximately day 200, but not a specific difference between the other visits. Salivary IL-8 was not associated with oral cGVHD activity after adjustment for study time and repeated observations. Accordingly, IL-8 did not identify concurrent oral cGVHD activity in this cohort.

The serum–saliva analyses addressed a separate question: whether a salivary concentration could be used to estimate the corresponding serum concentration. The models accounted for the fact that several samples could originate from the same patient and that biomarker concentrations could change over time. Under this approach, no association was observed between serum IgA and salivary sIgA or between serum and salivary IL-6 or IL-8. Thus, salivary measurements cannot replace serum measurements when the aim is to estimate the corresponding systemic biomarker concentration. This does not mean that salivary biomarkers lack clinical value; rather, serum and saliva may reflect different biological compartments and may be associated with different clinical features. For sIgA, the absence of a direct serum–saliva association is biologically plausible because secretory IgA is produced and transported through mucosal mechanisms distinct from serum IgA [50].

Higher oral cGVHD activity was associated with lower salivary sIgA after adjustment for study time and repeated measurements within patients. This direction agrees with previous reports of reduced salivary sIgA in patients with chronic GvHD [34].

In the present model, a 1-point higher NIH oral cGVHD activity score was associated with an approximately 71% lower expected salivary sIgA concentration. This finding was exploratory and was based on 37 observations from 21 patients. In particular, there were few observations with higher oral cGVHD activity scores, and none of the T4 observations included in the sIgA analysis had a score above 0. The estimated effect should therefore not be interpreted as evidence of a uniform linear decrease across the full score range. The analysis also cannot establish whether reduced sIgA precedes, accompanies, or follows oral cGVHD activity. No association with oral cGVHD activity was observed for salivary IL-6 or IL-8.

Several limitations should be considered. This was an exploratory study with a small cohort and decreasing biomarker availability over follow-up. Patients with samples available at later visits may not fully represent the baseline cohort. Sampling at four scheduled visits also cannot describe biomarker dynamics during the first 100 days after transplantation. A non-transplanted control group was not included. Finally, the serum–saliva and oral-cGVHD analyses were exploratory; effect estimates and their confidence intervals should therefore be considered together with p values. Larger prospective studies with standardized sampling and sufficient follow-up are needed to assess whether salivary sIgA can contribute to monitoring oral cGVHD activity.

Conclusions

During the first year after allo-HSCT, salivary sIgA and IL-8 showed time-dependent changes that remained robust in sensitivity analyses. A time effect was also observed for salivary IL-6 in the primary analysis, but this finding was not retained in sensitivity analysis and should therefore be interpreted cautiously. Salivary concentrations were not associated with their corresponding serum biomarkers after accounting for repeated measurements and study time. Higher post-transplant oral GvHD severity was associated with lower salivary sIgA, whereas no corresponding association was observed for IL-6 or IL-8. Overall, the findings demonstrate distinct longitudinal patterns in salivary immune markers after allo-HSCT and identify sIgA as a candidate marker warranting further prospective evaluation in standardized, adequately powered cohorts.

Declaratons

Declarations

Funding

No funding was received for conducting this study.

Competing interest

The authors declare that they have no competing interest.

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the State Chamber of Physicians of Rhineland-Palatinate (approval no. 873.205.06(5303)).

Consent to Participate

Written informed consent was obtained from all participants prior to their inclusion in the study.

Consent for Publication

Not applicable. The manuscript contains no identifiable individual participant information.

Data Availability

The datasets generated and analyzed during the current study are not publicly available due to patient confidentiality and data protection requirements. De-identified data may be made available from the corresponding author upon reasonable request, subject to institutional approval and applicable data protection regulations.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI, GPT-5.6 Sol) solely for English-language editing, including correction of grammar, spelling, and linguistic clarity.

Author Contributions

Solomiya Kyyak: Data curation, formal analysis, writing original draft, writing review and editing.

Eva Wagner-Drouet: Methodology, writing review and editing, supervision.

Julia Heider: Conceptualization, methodology, investigation, data curation, formal analysis, writing review and editing, supervision.

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Figures

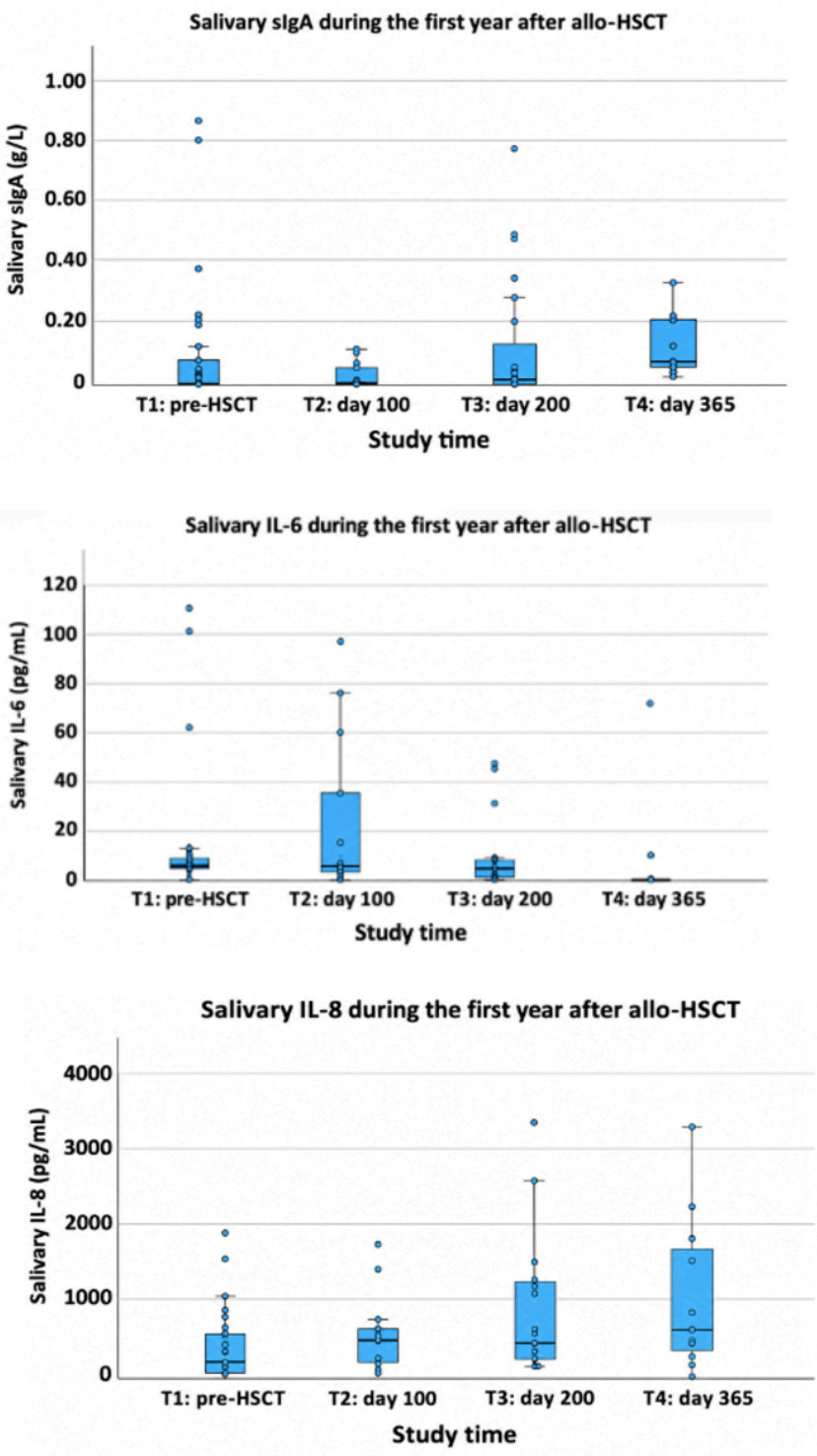

Figure 1

Distribution of salivary biomarker concentrations during the first year after allo-HSCT. sIgA, IL-6, and IL-8 at T1, T2, T3, and T4. Boxplots show the median and interquartile range and are overlaid with individual observations. The plots are descriptive; longitudinal inference was based on the repeated-measures GEE models.

Supplementary Files

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