

ACE2-CENTERED LONGITUDINAL DYNAMICS OF COMPLEMENT AND HYPOXIA-RELATED BIOMARKERS IN LONG COVID

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Aim. To characterize the longitudinal relationships of baseline ACE2 and within-patient ACE2 change with complement components C3 and C4 and the hypoxia-related biomarker HIF-1 α between 3 and 6 months after SARS-CoV-2 infection.

Materials and methods. This prospective longitudinal observational study included 69 patients with paired plasma samples collected at 3 and 6 months after COVID-19. Plasma concentrations of ACE2, C3, C4, and HIF-1 α were quantified using enzyme-linked immunosorbent assays. Longitudinal changes were evaluated using paired analyses and random-intercept mixed-effects models. Secondary analyses included baseline-adjusted regression, change-score associations, Pearson and Spearman correlations, and ACE2 trajectory evaluation. Robustness was assessed using raw and log-transformed variables, influential-observation analyses, alternative trajectory thresholds, and exploratory nonlinear ACE2 models. False-discovery-rate correction was applied to prespecified hypothesis families.

Results and discussion. ACE2, C3, C4, and HIF-1 α showed distinct longitudinal patterns between 3 and 6 months. Time-by-baseline-ACE2 interactions differed across the three biomarkers, with C4 showing the strongest ACE2-related signal, followed by C3 and HIF-1 α . Although the linear interaction terms did not remain statistically significant after false-discovery-rate correction, complementary baseline-adjusted and change-score analyses indicated differentiated complement and hypoxia-related responses. Sensitivity analyses identified C4 as the leading candidate for a complex ACE2-associated longitudinal pattern, including evidence of nonlinearity, whereas HIF-1 α showed pronounced temporal change with comparatively limited ACE2-centered association.

Conclusions. Complement and hypoxia-related biomarkers displayed distinct longitudinal behavior in relation to ACE2 during long COVID recovery. C4 showed the most prominent evidence of a potentially complex ACE2-associated pattern, while C3 and HIF-1 α demonstrated different longitudinal profiles. These findings indicate that post-COVID biomarker evolution is pathway specific and cannot be fully represented by a single uniform linear ACE2-centered mechanism.

Key words: ACE2; C3; C4; HIF-1 α ; complement system; hypoxia signaling; long COVID; longitudinal analysis; mixed-effects model; biomarker dynamics

INTRODUCTION

Long COVID, characterized by the persistence or development of symptoms beyond the acute phase of SARS-CoV-2 infection, represents a major challenge for global healthcare systems due to its heterogeneous clinical manifestations and complex biological mechanisms [1, 2]. Although many patients gradually recover after acute infection, a substantial proportion experience persistent clinical and biological abnormalities, highlighting the need to identify biomarkers that reflect underlying recovery trajectories and disease heterogeneity [3, 4].

Accumulating evidence indicates that long COVID involves persistent endothelial dysfunction, immune dysregulation, complement activation, and altered metabolic responses [5, 6, 7, 8]. The renin-angiotensin system, particularly angiotensin-converting enzyme 2 (ACE2), has attracted considerable attention because of its dual role as the cellular receptor for SARS-CoV-2 entry and as a critical regulator of vascular homeostasis, inflammation, and tissue repair [9, 10]. During SARS-CoV-2 infection, ACE2 dysregulation may contribute to endothelial injury, inflammatory imbalance, and persistent pathological

signaling through disruption of the ACE2/angiotensin-(1–7)/Mas receptor axis [11, 12]. However, the longitudinal behavior of ACE2 levels during recovery and its relationship with downstream immune and stress-response pathways remain incompletely understood.

The complement system is a key component of innate immunity and has been implicated in persistent inflammatory activation, endothelial injury, and thromboinflammatory responses following COVID-19 [13, 14]. Complement components C3 and C4 represent central elements of complement activation and regulation, with altered levels reflecting changes in immune homeostasis and inflammatory status [15]. In parallel, hypoxia-inducible factor 1- α (HIF-1 α) functions as a major regulator of cellular adaptation to hypoxic and metabolic stress and interacts with inflammatory pathways involved in persistent immune activation [16, 17]. The biological connections between ACE2, complement regulation, and hypoxia-related signaling suggest that these biomarkers may represent interconnected components of long-term post-COVID recovery.

Previous studies have demonstrated persistent inflammatory abnormalities, complement dysregulation, and heterogeneous biomarker signatures in long COVID; however, the longitudinal relationships between interconnected biological pathways remain incompletely characterized [18, 19, 20]. Individual biomarker analyses are valuable for identifying concentration changes but may not fully characterize whether different biological pathways follow coordinated or distinct recovery patterns. Therefore, investigating ACE2-centered longitudinal relationships with complement and hypoxia-related biomarkers may provide additional insight into the biological organization of long COVID recovery.

In this study, we hypothesized that ACE2 levels is associated with distinct longitudinal patterns of complement and hypoxia-related biomarkers during the recovery phase of COVID-19.

We aimed to characterize the longitudinal dynamics of ACE2, C3, C4, and HIF-1 α between 3 and 6 months after SARS-CoV-2 infection and to evaluate whether baseline ACE2 levels and ACE2 changes were associated with subsequent biomarker trajectories. Understanding these pathway-specific longitudinal patterns may provide a foundation for more comprehensive systems-level approaches to investigate persistent biological remodeling in long COVID.

MATERIALS AND METHODS

Study design and participants

This prospective longitudinal observational study included adults who had recovered from PCR-confirmed COVID-19 and were evaluated at two predefined follow-up points: 3 and 6 months after infection. Participants were recruited in Karaganda, Re-

public of Kazakhstan, between May and August 2021 after discharge from infectious disease hospitals.

The present investigation was derived from the same longitudinal post-COVID cohort previously examined through a broad multilayer analysis of biological and clinical interaction networks [21]. Whereas that study characterized system-wide correlation structures, conditional dependencies, and temporal network remodeling, the current study addressed a distinct and more focused question: whether baseline ACE2 and longitudinal ACE2 change were associated with the trajectories of complement components C3 and C4 and the hypoxia-related marker HIF-1 α . This targeted analysis was designed to characterize pathway-specific ACE2-centered dynamics as a foundation for broader systems-level interpretation.

The final analytical cohort consisted of 69 participants with complete paired measurements of ACE2, C3, C4, and HIF-1 α at both follow-up points. Eligible participants were adults older than 18 years who had recovered from mild, moderate, or severe COVID-19. Exclusion criteria included pregnancy or lactation, immunocompromised status, including HIV infection, and active malignancy. No healthy control group was included because the study was designed to evaluate within-patient biomarker changes and longitudinal associations during post-COVID recovery.

Clinical data

Clinical information related to the acute phase of COVID-19 was obtained from electronic medical records. Acute COVID-19 severity was classified according to World Health Organization clinical guidance as mild, moderate, or severe [22]. These data were used to characterize the clinical background of the cohort but were not included as primary predictors in the present ACE2-centered analysis.

Blood sampling and biomarker measurement

Venous blood was collected at the 3- and 6-month follow-up visits into EDTA-containing tubes. Samples were centrifuged at 1500–2000 $\times g$ for 10–15 min at 4° C, and the separated plasma was aliquoted and stored at –80° C until laboratory analysis.

Plasma concentrations of ACE2, C3, C4, and HIF-1 α were measured using commercial enzyme-linked immunosorbent assay kits according to the manufacturers' instructions. Optical density was measured at 450 nm, with reference-wavelength correction where required, and concentrations were calculated using four-parameter logistic standard curves. Standard calibrators and control samples were included in each assay, and the available intra-assay and inter-assay coefficients of variation did not exceed 10%.

Data preparation

The 3-month assessment was defined as baseline and the 6-month assessment as longitudinal follow-up. Within-patient change was calculated as the 6-month value minus the corresponding 3-month value.

Table 1 – Longitudinal characteristics of ACE2, C3, C4, and HIF-1 α in the paired cohort (n=69)

Biomarker	3 months, mean $\pm$ SD	6 months, mean $\pm$ SD	Mean change	Median change	Effect size	FDR- adjusted p	Direction across participants
ACE2 (U/L)	0.639 $\pm$ 0.251	14.307 $\pm$ 8.270	+13.668	+9.047	1.000	<0.001	69 increased; 0 decreased
C3 (mg/dL)	1.371 $\pm$ 0.516	50.568 $\pm$ 23.183	+49.198	+44.197	2.170	<0.001	69 increased; 0 decreased
C4 (mg/dL)	1.413 $\pm$ 0.440	0.613 $\pm$ 0.421	-0.800	-0.686	-0.936	<0.001	10 increased; 59 decreased
HIF-1 α (pg/mL)	0.042 $\pm$ 0.164	0.095 $\pm$ 0.287	+0.052	+0.037	1.000	<0.001	69 increased; 0 decreased

Note: Values are presented in original laboratory units. ACE2 and HIF-1 α were compared using Wilcoxon signed-rank tests; C3 and C4 were compared using paired t-tests. Effect sizes are those reported by the analytical pipeline. FDR adjustment was applied across the four paired longitudinal comparisons

Original laboratory values were retained for descriptive summaries and paired longitudinal comparisons. Baseline ACE2 was standardized before inclusion as the principal predictor in the longitudinal models, allowing its coefficient to represent the expected outcome difference associated with a one-standard-deviation higher ACE2 level at baseline. C3, C4, and HIF-1 α were treated as the prespecified outcome biomarkers.

Statistical analysis

Continuous variables were summarized using means and standard deviations and medians and interquartile ranges, as appropriate. Longitudinal changes between 3 and 6 months were evaluated using paired-samples t-tests when within-patient differences were approximately normally distributed and Wilcoxon signed-rank tests when the normality assumption was not satisfied.

The primary analysis used random-intercept linear mixed-effects models to determine whether standardized baseline ACE2 was associated with different longitudinal trajectories of C3, C4, and HIF-1 α . Separate models were fitted for each outcome and included time, standardized baseline ACE2, and the time-by-baseline-ACE2 interaction. The interaction term was the principal parameter of interest because it evaluated whether biomarker changes between 3 and 6 months differed according to baseline ACE2 level.

Secondary analyses included baseline-adjusted regression models, associations between ACE2 change and changes in C3, C4, and HIF-1 α , and Pearson and Spearman correlation analyses. Heteroscedasticity-consistent HC3 standard errors were used for the secondary regression models. Sensitivity analyses examined raw and log-transformed values,

influential observations, alternative ACE2 trajectory thresholds, and exploratory nonlinear ACE2 terms.

The Benjamini – Hochberg false discovery rate procedure was applied separately within prespecified hypothesis families to account for multiple testing [23]. All statistical tests were two-sided, with $p < 0.05$ considered nominally significant. Principal interpretation was based on FDR-adjusted results, while unadjusted results were used to characterize exploratory signals. Analyses were conducted using Python 3.10.12 with pandas, NumPy, SciPy, statsmodels, scikit-learn, and Matplotlib.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki [24] and was approved by the Bioethics Committee of Karaganda Medical University, Republic of Kazakhstan, Protocol No. 18 dated 14 April 2021. Written informed consent was obtained from all participants before enrollment.

RESULTS

Longitudinal Changes in ACE2, C3, C4, and HIF-1 α

The longitudinal analysis included 69 participants with complete paired measurements at both 3 and 6 months after COVID-19. The four biomarkers followed clearly differentiated temporal patterns, indicating that endothelial/RAS, complement, and hypoxia-related pathways did not evolve uniformly during follow-up.

ACE2 increased markedly from 0.639 $\pm$ 0.251 U/L at 3 months to 14.307 $\pm$ 8.270 U/L at 6 months. C3 also increased substantially, from 1.371 $\pm$ 0.516 to 50.568 $\pm$ 23.183 mg/dL. In contrast, C4 decreased from 1.413 $\pm$ 0.440 to 0.613 $\pm$ 0.421 mg/dL. HIF-1 α in-

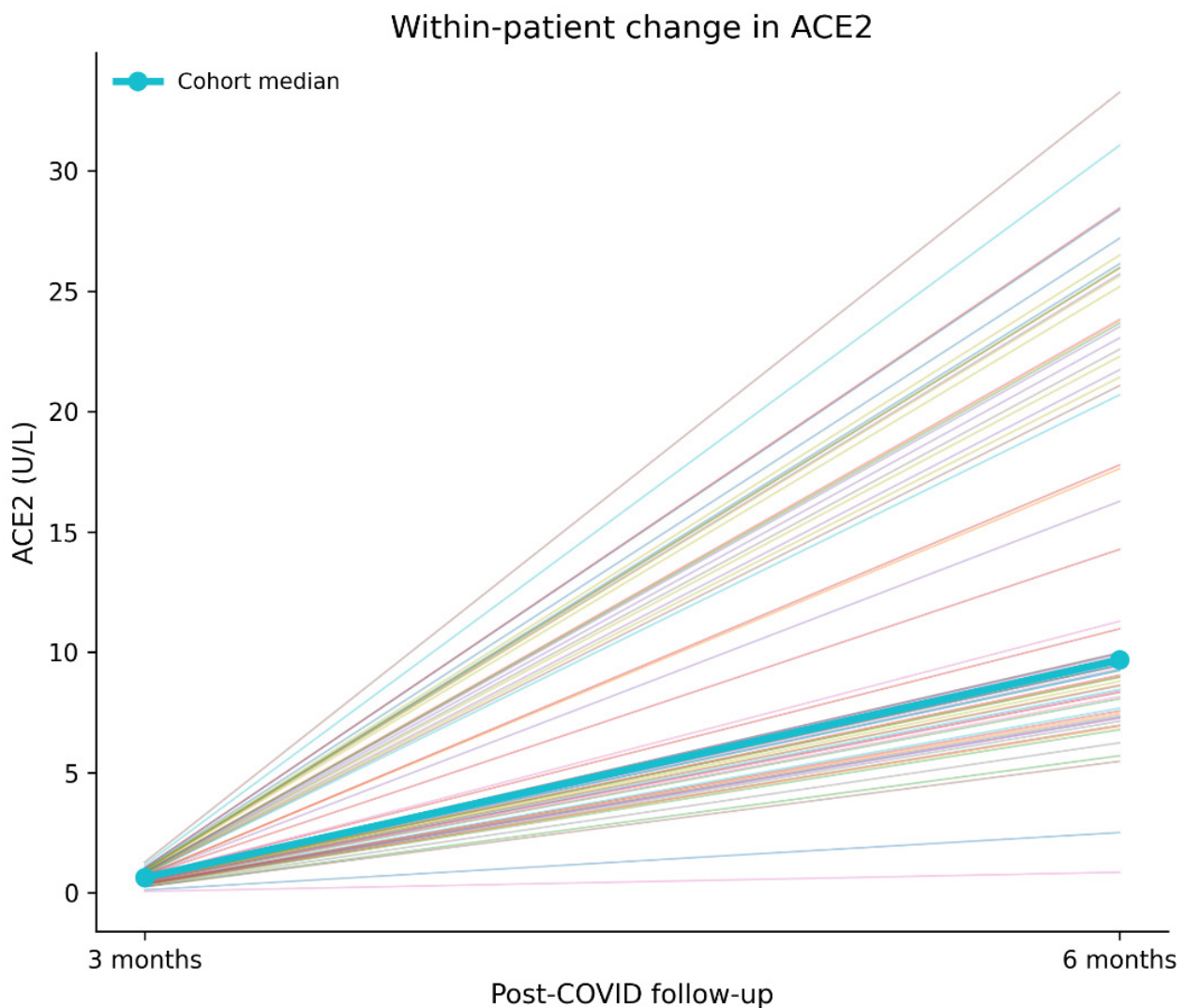


Figure 1 – Within-patient ACE2 trajectories between 3 and 6 months after COVID-19. Individual lines represent paired observations for each participant

Table 2 – Primary mixed-effects models for the time-by-baseline-ACE2 interaction

Outcome	Interaction coefficient (β)	SE	95% CI	Nominal p	FDR-adjusted p	Result pattern
C3	-3.514	2.726	-8.856 to 1.829	0.197	0.296	Weak negative interaction estimate
C4	-0.158	0.073	-0.301 to -0.016	0.030	0.089	Strongest primary ACE2-related signal
HIF-1 α	0.011	0.015	-0.019 to 0.040	0.482	0.482	Limited interaction estimate

Note: Separate random-intercept models were fitted for each outcome. Baseline ACE2 was standardized. The coefficient shown corresponds to the time [T.short] $\times$ baseline ACE2 contrast used in the primary output; therefore, its sign must be interpreted according to that coding. FDR correction was applied across the three prespecified interaction tests

creased from 0.042 ± 0.164 to 0.095 ± 0.287 pg/mL. All four longitudinal changes remained statistically significant after false-discovery-rate correction (Table 1).

The direction-of-change analysis showed that ACE2, C3, and HIF-1 α increased in all 69 participants. C4 decreased in 59 participants and increased

in 10. Thus, the observed group-level differences reflected broadly distributed within-patient changes rather than differences between unrelated cross-sectional samples. The individual ACE2 trajectories are shown in Figure 1, while Figure 2 presents the paired changes in all four biomarkers.

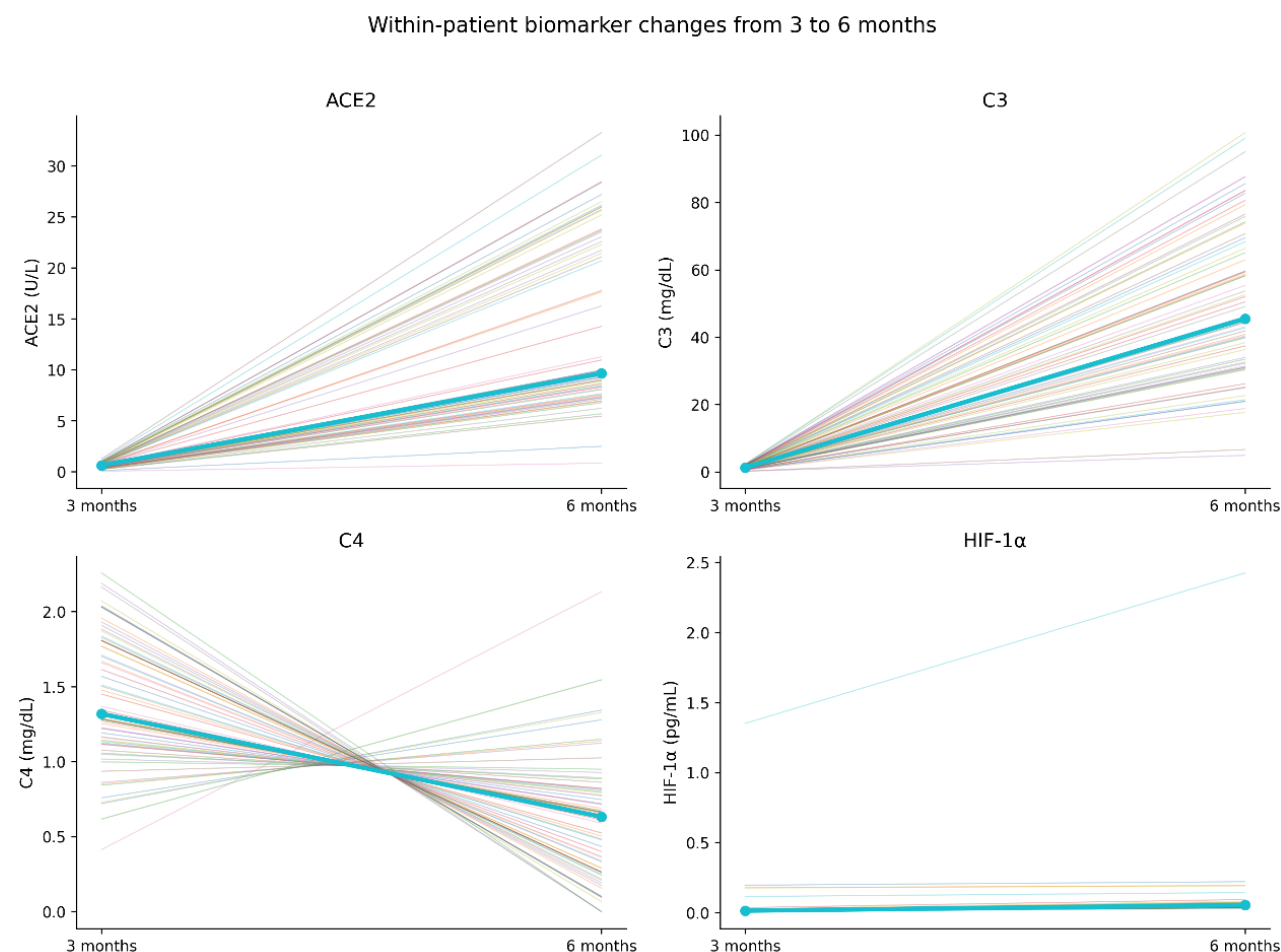


Figure 2 – Paired longitudinal changes in ACE2, C3, C4, and HIF-1α between 3 and 6 months after COVID-19

Table 3 – Integrated secondary ACE2-centered findings

Outcome	Baseline ACE2 β	FDR p	ACE2-change β	FDR p	Pearson r	Spearman ρ	Comparative pattern
C3	-1.077	0.234	1.525	0.092	0.132	0.153	Strongest baseline-adjusted ACE2-change signal
C4	-0.037	0.234	0.053	0.107	0.220	0.158	Strongest direct change-to-change correlation
HIF-1α	0.006	0.581	-0.013	0.428	-0.092	-0.143	Distinct, comparatively weak ACE2-centered pattern

Note: Baseline-adjusted models included the corresponding 3-month outcome, standardized baseline ACE2, and standardized ACE2 change, with HC3 robust standard errors. FDR values for baseline ACE2 and ACE2 change were calculated within separate hypothesis families. Correlations are based on within-patient change scores

Baseline ACE2 and longitudinal biomarker trajectories

The primary mixed-effects analysis examined whether the longitudinal trajectories of C3, C4, and HIF-1α differed according to baseline ACE2. Separate random-intercept models were fitted for each

outcome, and the time-by-baseline-ACE2 interaction was the principal parameter of interest.

The interaction estimates differed across the three biomarkers (Table 2). For C3, the interaction coefficient was -3.514 (95% CI: -8.856 to 1.829), indicating a weaker longitudinal increase at high-

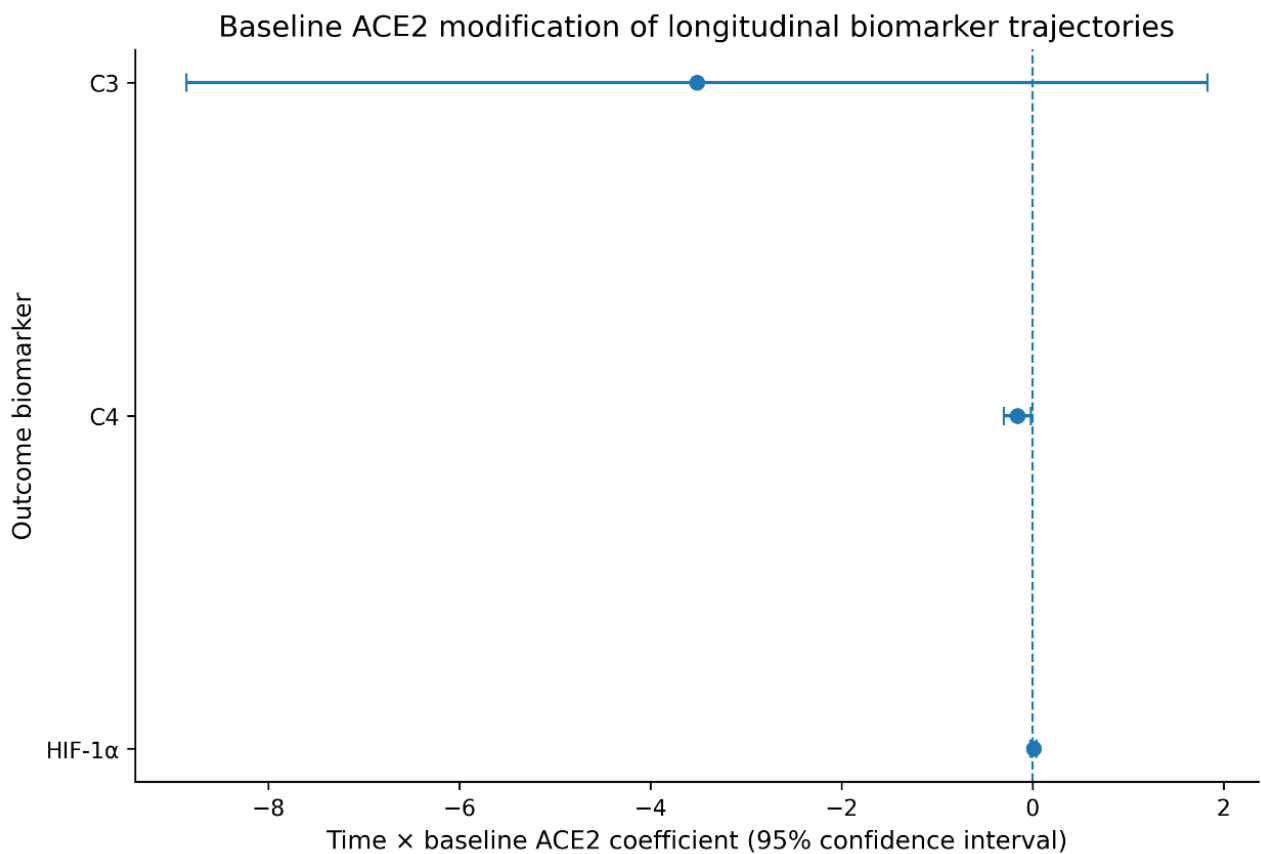


Figure 3 – Forest plot of the time-by-baseline-ACE2 interaction estimates for C3, C4, and HIF-1α

Table 4 – Robustness and model-form comparison

Outcome	Primary linear FDR p	Raw-scale β (p)	Log-scale β (p)	Influential-case result	Quadratic β (p)	Integrated result pattern
C3	0.296	3.514 (0.197)	–0.001 (0.953)	Unchanged; no exclusions	4.359 (0.036)	Weak linear evidence; exploratory nonlinear signal
C4	0.089	0.158 (0.030)	0.048 (0.677)	Unchanged; no exclusions	0.198 (<0.001)	Strongest but scale-sensitive complex pattern
HIF-1α	0.482	–0.011 (0.482)	–0.035 (0.236)	Unchanged; no exclusions	–0.005 (0.653)	Limited linear and nonlinear ACE2-centered evidence

Note: Raw- and log-scale sensitivity coefficients use the long-minus-short contrast and therefore have the opposite sign from the primary table, which reports the short-minus-long contrast. Nonlinear models were exploratory and were not used to replace the prespecified primary linear models

er baseline ACE2 values under the model contrast; however, the confidence interval included zero and the FDR-adjusted p-value was 0.296. HIF-1α showed a small positive interaction coefficient of 0.011 (95% CI: –0.019 to 0.040; FDR-adjusted p=0.482), indicating comparatively limited differentiation of its trajectory by baseline ACE2.

C4 produced the strongest primary ACE2-related signal. Its interaction coefficient was –0.158 (95% CI: –0.301 to –0.016), with a nominal p-value of 0.030

and an FDR-adjusted p-value of 0.089. Although this result did not cross the prespecified FDR threshold, its magnitude and narrower confidence interval distinguished C4 from C3 and HIF-1α. The estimates and their uncertainty are visualized in Figure 3.

Complementary ACE2-Centered Associations

Secondary baseline-adjusted models evaluated whether baseline ACE2 and within-patient ACE2 change were associated with 6-month C3, C4, and HIF-1α after accounting for the corresponding

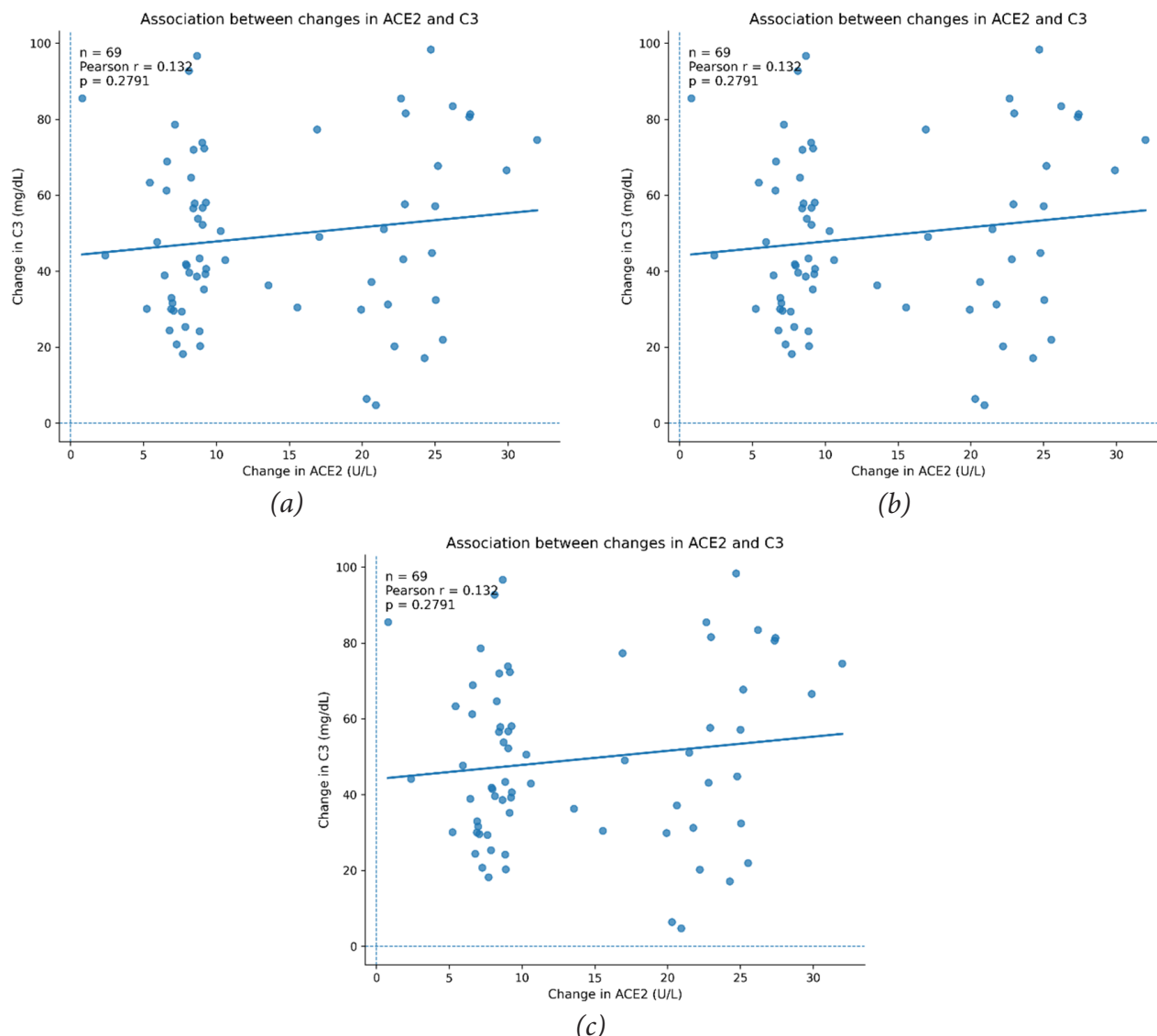


Figure 4 – Associations between changes in ACE2 and changes in (a) C3, (b) C4, and (c) HIF-1 α between 3 and 6 months after COVID-19. Solid lines represent linear regression fits, and dotted horizontal and vertical lines indicate zero change

3-month biomarker value. This analysis separated the potential contribution of the initial ACE2 state from the contribution of ACE2 evolution during follow-up. These findings are summarized in Table 3.

Baseline ACE2 showed negative coefficients for C3 and C4 and a small positive coefficient for HIF-1 α , but none remained significant after FDR correction. ACE2 change produced more prominent positive coefficients for both complement components. The strongest baseline-adjusted change signal was observed for C3 ($\beta=1.525$; FDR-adjusted $p=0.092$), followed by C4 ($\beta=0.053$; FDR-adjusted $p=0.107$). HIF-1 α showed a small negative coefficient for ACE2 change ($\beta= -0.013$; FDR-adjusted $p=0.428$).

Direct change-score correlations showed the same pathway distinction. ACE2 change was positively correlated with changes in C3 and C4, with the largest Pearson correlation observed for C4 ($r=0.220$),

whereas the relationship with HIF-1 α change was weakly negative ($r= -0.092$). Pearson and Spearman estimates were similar in direction, suggesting that the overall pattern was not dependent on a single correlation method. The three change-score relationships are illustrated in Figure 4.

Robustness and Exploratory Nonlinear Patterns

Sensitivity analyses assessed whether the primary findings depended on measurement scale, influential observations, or model form (Table 4). The influential-observation analysis identified no participants requiring exclusion; consequently, estimates from the complete-cohort and exclusion models were identical.

Transformation sensitivity was most evident for C4. In the raw-scale model using the long-minus-short contrast, the time-by-baseline-ACE2 coefficient was 0.158 ($p=0.030$), whereas the corresponding log-scale coefficient was 0.048 ($p=0.677$). C3 and

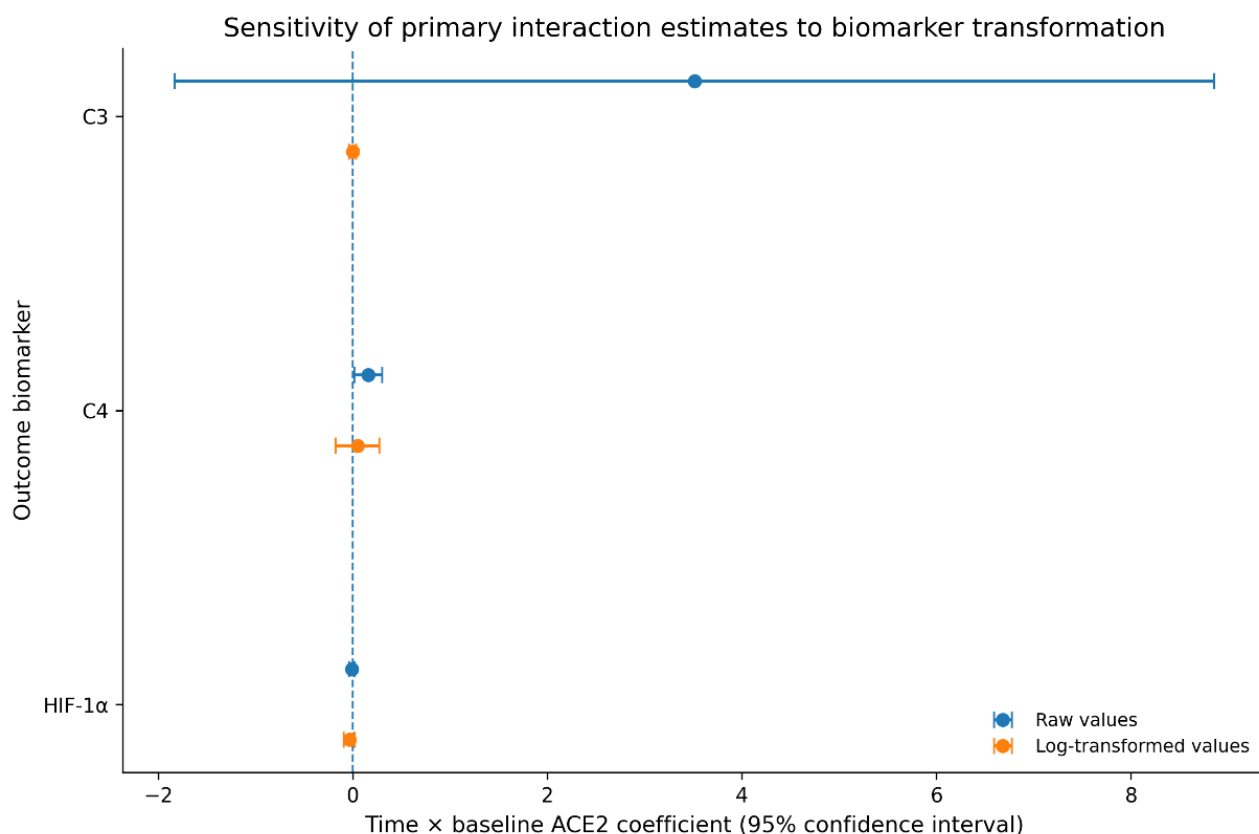


Figure 5 – Sensitivity of the time-by-baseline-ACE2 interaction estimates to raw and log-transformed biomarker values

HIF-1 α also showed attenuation or changes in magnitude after logarithmic transformation. These results indicate that the strength of the simple linear association depended partly on the analytical scale, particularly for C4.

Exploratory nonlinear models provided a complementary pattern. Significant quadratic time-by-baseline-ACE2 terms were observed for C3 ($\beta=4.359$; $p=0.036$) and C4 ($\beta=0.198$; $p<0.001$), with the strongest evidence again observed for C4. No comparable nonlinear pattern was identified for HIF-1 α ($p=0.653$). These exploratory results suggest that complement-related longitudinal behavior may vary across the baseline ACE2 distribution rather than following one uniform straight-line relationship. Figure 5 summarizes transformation sensitivity.

DISCUSSION

The present study delineates a heterogeneous pattern of longitudinal biomarker remodeling during post-COVID recovery. Although ACE2, C3, and HIF-1 α increased between 3 and 6 months whereas C4 decreased, the principal finding extends beyond these temporal shifts: the relationships of C3, C4, and HIF-1 α with ACE2 were not concordant across the analytical framework. C4 was distinguished by the time-by-baseline-ACE2 interaction and by the exploratory nonlinear analysis; C3 was distinguished in

the baseline-adjusted analysis of ACE2 change; and HIF-1 α exhibited substantial temporal variation with comparatively limited ACE2-centered association. Taken together, these findings indicate that post-COVID biomarker evolution is organized in a pathway-specific manner rather than according to a single uniform ACE2-centered trajectory.

The longitudinal increase in circulating ACE2 is relevant to the persistent involvement of the renin–angiotensin system and vascular endothelium after acute SARS-CoV-2 infection. ACE2 occupies a central position at the interface of viral entry, vascular homeostasis, and inflammatory regulation, while contemporary evidence continues to implicate endothelial dysfunction and endothelial inflammatory signaling in long COVID and post-COVID organ injury [25,26]. In the present cohort, however, the increase in ACE2 was accompanied by divergent responses in complement and hypoxia-related biomarkers. This dissociation argues against interpreting circulating ACE2 as a uniform index of biological recovery and instead supports its evaluation within the context of specific downstream pathways.

The complement findings further underscore the heterogeneity of post-COVID biomarker remodeling. C3 and C4 evolved in opposite directions during follow-up, demonstrating that individual complement components need not exhibit parallel longitudinal be-

havior within the same participants. The divergent longitudinal behavior of C3 and C4 is concordant with the growing body of evidence implicating persistent complement dysregulation in long COVID. Activation of classical, alternative, and terminal complement pathways in association with thromboinflammatory abnormalities has been documented in active long COVID [27], and complement-associated inflammatory signatures have also been identified across distinct clinical phenotypes [28, 29]. At the same time, systematic evidence indicates substantial heterogeneity across studies evaluating complement-related biomarkers [30]. The present paired longitudinal data add to this literature by demonstrating that C3 and C4 can follow divergent trajectories during the same interval of post-COVID recovery.

C4 showed the clearest evidence of a baseline-ACE2-related longitudinal pattern. In the primary mixed-effects analysis, C4 was the only outcome for which the time-by-baseline-ACE2 interaction reached nominal statistical significance, although the association did not remain significant after FDR correction. The sensitivity analyses further demonstrated attenuation of the linear signal after logarithmic transformation, whereas the exploratory quadratic model identified a significant nonlinear time-by-ACE2 term. This combination of findings indicates that the ACE2–C4 relationship is not adequately represented by a single scale-independent linear effect. The appropriate interpretation is therefore not one of established ACE2–C4 coupling, but of an analytical pattern that warrants further investigation of nonlinear endothelial/RAS–complement relationships.

C3 exhibited a different pattern. In the baseline-adjusted secondary analysis, the ACE2-change term for C3 yielded the lowest FDR-adjusted p value within the corresponding prespecified hypothesis family, whereas the direct change-score analysis showed a positive ACE2–C3 relationship and the largest Pearson correlation was observed for C4. These results distinguish the information contained in baseline ACE2 from that contained in its within-patient change. For C3, the analytical pattern places greater emphasis on concurrent ACE2 evolution than on the ACE2 concentration measured at the beginning of follow-up. Although the secondary association did not satisfy the FDR-adjusted significance criterion, it provides a coherent change-related signal that complements the baseline-ACE2 findings observed for C4.

HIF-1 α was differentiated from both complement components. Despite a significant longitudinal increase, neither baseline ACE2 nor ACE2 change showed a substantial association with its trajectory. The dissociation between the marked temporal increase in HIF-1 α and its limited association with ACE2 indicates that temporal biomarker evolution and ACE2-centered organization represent distinct biological dimensions. HIF-1 α is positioned at the

intersection of hypoxic, metabolic, and inflammatory signaling, and its temporal behavior therefore reflects a biological dimension that is at least partly distinct from the endothelial/RAS axis. The weak negative change-score relationship for HIF-1 α , in contrast to the positive directions observed for C3 and C4, further reinforces this separation.

Viewed collectively, the findings support a model of post-COVID recovery characterized by differentiated, time-dependent organization across interconnected biological pathways. The contribution of the present analysis lies not solely in documenting longitudinal concentration changes, but in demonstrating that the relationship of each outcome biomarker with ACE2 depends on both the biological pathway and the analytical dimension examined. This interpretation is concordant with the broader systems-level analysis of the same cohort, which demonstrated temporal reorganization of immune, endothelial/RAS, oxidative-redox, and hypoxia-related interactions, together with relative stability of the psychometric–autonomic cluster and marked changes in C3–C4 and ACE2–C4 relationships [21]. Together, these complementary analyses support an integrated view of long COVID in which recovery is defined by evolving interrelationships among biological systems rather than by isolated biomarker trajectories or a single common linear mechanism.

Limitations. The findings should be interpreted within the scope of the present longitudinal observational design. The study focused on circulating biomarker dynamics and ACE2-centered associations during post-COVID recovery; therefore, mechanistic interpretation remains limited to the biological pathways represented by the measured variables. Further studies incorporating additional molecular and clinical dimensions would help extend and validate these longitudinal patterns.

Novelty of the study. The principal novelty of this study lies in its analytical design, which evaluates ACE2 simultaneously as a baseline modifier of longitudinal biomarker trajectories and as a dynamic within-patient variable. By integrating paired biomarker change, time-by-baseline-ACE2 interactions, and associations between ACE2 change and subsequent biomarker behavior, the study provides a focused framework for distinguishing pathway-specific longitudinal relationships that are not captured by conventional cross-sectional or single-time-point analyses. An additional contribution is the direct comparison of baseline-dependent and change-dependent ACE2 relationships within the same cohort and follow-up interval, allowing these two dimensions of biological variation to be evaluated separately rather than treated as interchangeable. The inclusion of sensitivity analyses and exploratory nonlinear modeling further extends the framework by testing whether observed ACE2-centered patterns remain consistent across

alternative model specifications. Together, this design provides a more refined longitudinal approach for investigating heterogeneous biomarker regulation during post-COVID recovery.

Translational significance. From a translational perspective, the findings support further evaluation of longitudinal endothelial/RAS-complement interactions in long COVID. Complement-related pathways remain clinically relevant because complement activation markers have been associated with active long COVID and have been investigated as potential therapeutic targets [27, 29, 31]. However, the present findings are not sufficient to support diagnostic, prognostic, or treatment-selection use of ACE2, C3, C4, or HIF-1 α . Future studies should determine whether these longitudinal patterns improve clinical phenotyping, prognostic stratification, or identification of biologically defined patient subgroups.

CONCLUSIONS

The present study demonstrates that longitudinal post-COVID biomarker dynamics are characterized by differentiated relationships between ACE2, complement components, and HIF-1 α rather than by a uniform pattern of change. The findings distinguish baseline-dependent and within-patient ACE2-related effects across these pathways and indicate that complement and hypoxia-associated responses evolve according to different biological trajectories during follow-up.

The results further emphasize the importance of analytical context in interpreting longitudinal biomarker behavior. The C4 pattern indicates that ACE2-related complement dynamics are not adequately represented by a simple linear relationship, while the C3 findings highlight the relevance of within-patient ACE2 change. In contrast, HIF-1 α follows a more distinct temporal course with limited ACE2-centered association. These differences reinforce the concept that post-COVID recovery involves pathway-specific biological remodeling rather than synchronized evolution across all measured systems.

Collectively, the study refines the understanding of ACE2-centered post-COVID biology by demonstrating that the biological significance of ACE2 depends on both the pathway examined and the longitudinal dimension considered. This framework provides a more precise basis for interpreting post-COVID biomarker evolution and for identifying biologically distinct patterns that may not be evident from single-time-point measurements alone. Further longitudinal studies should extend these findings across broader patient populations, incorporate additional clinical and molecular dimensions, and evaluate their prognostic and translational relevance over longer periods of follow-up.

Authors' contributions:

L. N. Vajdi – conceptualization, writing – original draft preparation.

O. A. Ponamareva – methodology.

D. A. Klyuyev – validation, resources, supervision, project administration.

L. N. Vajdi, A. M. Vajdi – formal analysis, visualization.

D. A. Klyuyev, L. N. Vajdi – investigation.

L. N. Vajdi, D. A. Klyuyev, O. A. Ponamareva, A. M. Vajdi – data curation.

D. A. Klyuyev, O. A. Ponamareva – writing – review and editing.

Conflict of interests:

The authors declare that there is no conflict of interests regarding the publication of this paper.

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АСЕ2-ЦЕНТРИРОВАННАЯ ПРОДОЛЬНАЯ ДИНАМИКА КОМПОНЕНТОВ КОМПЛЕМЕНТА И ГИПОКСИЯ-АССОЦИИРОВАННЫХ БИОМАРКЕРОВ ПРИ ДЛИТЕЛЬНОМ COVID

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Цель исследования. Изучить связь исходного уровня ACE2 и его изменений в динамике с изменениями уровней компонентов комплемента C3 и C4 и гипоксия-ассоциированного биомаркера HIF-1α в период с 3 по 6 месяц после инфекции SARS-CoV-2.

Материалы и методы. В проспективное продольное наблюдательное исследование были включены 69 пациентов, у которых образцы плазмы крови были получены через 3 и 6 мес. после COVID-19. Концентрации ACE2, C3, C4 и HIF-1α в плазме определяли методом иммуноферментного анализа. Изменения показателей в динамике оценивали с использованием методов анализа парных данных и моделей смешанных эффектов со случайным интерсептом. Дополнительный анализ включал в себя регрессионные модели с поправкой на исходные значения, анализ взаимосвязей между изменениями показателей, корреляционный анализ Пирсона и Спирмена, а также оценку траекторий ACE2. Устойчивость результатов проверяли с использованием исходных и логарифмически преобразованных значений, анализа влиятельных наблюдений, альтернативных пороговых значений траекторий и исследовательских нелинейных моделей ACE2. Для заранее определенных групп гипотез применяли коррекцию на множественные сравнения с контролем частоты ложных открытий (FDR).

Результаты и обсуждение. В период с 3 по 6 месяц ACE2, C3, C4 и HIF-1α демонстрировали различную динамику. Характер взаимодействия времени и исходного уровня ACE2 различался для трех биомаркеров: наиболее выраженный сигнал связи с ACE2 наблюдался для C4, затем для C3 и HIF-1α. Хотя после FDR-коррекции линейные эффекты взаимодействия не сохраняли статистической значимости, дополнительные анализы с поправкой на исходные значения и анализ изменений показателей указывали на различия между динамикой компонентов системы комплемента и гипоксия-ассоциированного биомаркера. Анализ чувствительности показал, что наиболее выраженные признаки сложной, в том числе нелинейной, связи с ACE2 характерны для C4, тогда как HIF-1α демонстрировал выраженные изменения во времени при сравнительно слабой связи с ACE2.

Выводы. Компоненты системы комплемента и гипоксия-ассоциированный биомаркер HIF-1α характеризовались различной динамикой и неодинаковой связью с ACE2 в период восстановления после длительного COVID. Наиболее выраженные признаки потенциально сложной связи с ACE2 были выявлены для C4, тогда как C3 и HIF-1α демонстрировали иные варианты динамики. Результаты свидетельствуют о том, что изменения биомаркеров в постковидный период зависят от конкретного биологического пути и не могут быть полностью объяснены единым линейным ACE2-центрированным механизмом.

Ключевые слова: ACE2; C3; C4; HIF-1α; система комплемента; гипоксический сигналинг; длительный COVID; продольный анализ; модель смешанных эффектов; динамика биомаркеров

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ҰЗАҚ COVID КЕЗІНДЕГІ КОМПЛЕМЕНТ КОМПОНЕНТТЕРІ МЕН ГИПОКСИЯҒА БАЙЛАНЫСТЫ БИОМАРКЕРЛЕРДІҢ ACE2-ОРТАЛЫҚТАНДЫРЫЛҒАН БОЙЛЫҚ ДИНАМИКАСЫ

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Зерттеудің мақсаты. SARS-CoV-2 инфекциясынан кейінгі 3–6 ай аралығында ACE2-нің бастапқы деңгейі мен оның өзгерістерінің комплементтің C3 және C4 компоненттері және гипоксиямен байланысты HIF-1α биомаркері деңгейлерінің өзгеруімен байланысын зерттеу.

Материалдар және әдістер. Проспективті бойлық бақылаулық зерттеуге COVID-19-дан кейін 3 және 6 айда плазма үлгілері алынған 69 пациент енгізілді. Плазмадағы ACE2, C3, C4 және HIF-1α концентрациялары иммуноферменттік талдау әдісімен анықталды. Көрсеткіштердің уақыт бойынша өзгерістері жұпталған деректерді талдау әдістері және кездейсоқ интерсепті бар аралас әсерлер модельдері арқылы бағаланды. Қосымша талдау бастапқы мәндерге түзетілген регрессиялық модельдерді, көрсеткіштер өзгерістерінің өзара байланысын бағалауды, Пирсон және Спирмен корреляциялық талдауын, сондай-ақ ACE2 траекторияларын бағалауды қамтыды. Нәтижелердің тұрақтылығы бастапқы және логарифмдік түрлендірілген мәндерді, ықпалды бақылауларды талдауды, траекториялардың баламалы шекті мәндерін және ACE2-нің зерттеушілік сызықтық емес модельдерін қолдану арқылы тексерілді. Алдын ала белгіленген гипотезалар топтары үшін жалған ашылымдар жиілігін бақылау (FDR) әдісімен көптік салыстыруларға түзету енгізілді.

Нәтижелер және талқылау. 3 және 6 ай аралығында ACE2, C3, C4 және HIF-1α көрсеткіштерінің динамикасы әртүрлі болды. Уақыт пен ACE2-нің бастапқы деңгейінің өзара әсері үш биомаркер үшін ерекшеленді: ACE2-мен байланысты ең айқын белгі C4 үшін, одан кейін C3 және HIF-1α үшін байқалды. FDR-түзетуінен кейін сызықтық өзара әсерлер статистикалық маңыздылығын сақтамағанымен, бастапқы мәндерге түзетілген қосымша талдаулар мен көрсеткіштер өзгерістерін бағалау комплемент жүйесі мен гипоксияға байланысты биомаркер динамикасының ерекшеленетінін көрсетті. Сезімталдық талдауы C4 үшін ACE2-мен күрделі, соның ішінде сызықтық емес байланыстың ең айқын белгілерін анықтады, ал HIF-1α уақыт бойынша айқын өзгергенімен, оның ACE2-мен байланысы салыстырмалы түрде әлсіз болды.

Қорытынды. Комплемент компоненттері мен гипоксияға байланысты HIF-1α биомаркері ұзақ COVID-тен кейінгі қалпына келу кезеңінде әртүрлі динамика және ACE2-мен әртүрлі байланыс көрсетті. ACE2-мен ықтимал күрделі байланыстың ең айқын белгілері C4 үшін анықталды, ал C3 пен HIF-1α басқа динамикалық ерекшеліктермен сипатталды. Нәтижелер постковидтік кезеңдегі биомаркерлер өзгерістерінің нақты биологиялық жолға байланысты екенін және оларды бірыңғай сызықтық ACE2-орталықтандырылған механизммен толық түсіндіру мүмкін еместігін көрсетеді.

Кілт сөздер: ACE2; C3; C4; HIF-1α; комплемент жүйесі; гипоксиялық сигнал беру; ұзақ COVID; бойлық талдау; аралас әсерлер моделі; биомаркерлер динамикасы