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Association of Visceral and Subcutaneous Fat with COVID-19 Severity and Clinical Outcomes in Hospitalized Patients

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Abstract

Background: Obesity's connection to COVID-19 severity has prompted an investigation into its impact on the immune system. This study explores the relationship between visceral and subcutaneous fat and disease outcomes in COVID-19 patients.

Methods: The study involved 318 hospitalized COVID-19 patients, including 161 women. Lung CT scans assessed lung involvement and measured visceral and subcutaneous fat levels. The ratio of visceral fat to subcutaneous fat was calculated. Patient files were reviewed for ICU admission and mortality rates. SPSS16 software was used for data analysis.

Results: Age significantly influenced disease outcomes ($p=0.001$). Men had higher mean visceral fat (117.55 ± 51.56), while women had higher mean subcutaneous fat (175.93 ± 79.79) ($p<0.001$). The over-50 age group had significantly higher mean visceral fat ($p=0.021$). Higher mean visceral and subcutaneous fat correlated with longer hospital stays ($p<0.05$). However, no significant associations were found between fat measures, lung involvement severity, ICU admission, or mortality ($p>0.05$).

Conclusion: Age was significantly linked to disease severity and mortality in hospitalized COVID-19 patients. Visceral fat correlated with longer hospital stays, but not with lung involvement, ICU admission, or mortality. High lung involvement was associated with greater subcutaneous fat, but not significantly. Subcutaneous fat levels were lower in ICU patients and had lower mortality rates, although not statistically significant.

Keywords
COVID-19; Visceral adipose tissue (VAT); Subcutaneous adipose tissue (SAT); Obesity.

Core tip: This study examines the impact of visceral and subcutaneous fat on disease outcomes in 318 hospitalized COVID-19 patients. It highlights that age is a significant factor influencing disease severity and mortality. While men had higher visceral fat and women had higher subcutaneous fat, higher levels of both types of fat were linked to longer hospital stays. However, no significant associations were found between fat measures and lung involvement severity, ICU admission, or mortality. These findings suggest that age and fat distribution play roles in COVID-19 outcomes, but their impact on critical metrics like ICU admission and mortality is limited.

Introduction
In December 2019, we witnessed the emergence of a new form of the disease caused by the coronavirus called the COVID-19 disease, which has become the pandemic of the century in a short period and has affected almost all the societies of the world. The spread of acute respiratory syndrome of the SARS-CoV-2, which emerged in Wuhan, has rapidly spread throughout China and has become a global health threat [1-4].

Although most patients are either asymptomatic or have only a mild flu-like illness, a significant proportion have severe symptoms. However, the factors leading to the severity of the disease are unclear. Hence, careful investigation of factors associated with severe COVID-19 is needed [5-7]. As the epidemic was moving outside of China, there was a need to confirm the clinical characteristics and lethality of COVID-19 in countries with demographic characteristics [5]. This has led to research efforts around the world to identify those at greatest risk of serious illness and death. Preliminary data refer to older people as well as those with diabetes or cardiovascular including high blood pressure, and respiratory or kidney disease. These problems are often concentrated in certain racial groups (eg, African Americans and Asians), who appear to be more vulnerable to worse outcomes from COVID-19 [8].

Recent studies have identified several risk factors that predispose patients to severe disease. These include age, male gender, diabetes mellitus, high blood pressure, cardiopulmonary diseases, and obesity [2,8-10]. One of the important background factors that several studies emphasized is obesity [8,11,12]. The prevalence of obesity is increasing, especially in developed or developing countries. This issue is especially felt during the COVID-19 pandemic. On the other hand, studies indicate a close relationship between the occurrence of obesity and the severity of cardiometabolic events, the exacerbation of inflammatory processes, and the need to use a ventilator in patients with COVID-19 [7,13].

Obesity is also related to disorders of the body's immune systems, increasing the risk of metabolic

disorders such as diabetes and cardiovascular diseases, and therefore, the occurrence of various infectious and inflammatory consequences after contracting COVID-19 in obese patients is much more expected than in non-obese patients [14].

Not all body fat stores are created equal. In fact, the amount and distribution of body fat can have a significant impact on the immune system. Fats carry different cardiovascular and metabolic risks [9,15]. Fats have a high ability to accumulate in skeletal muscles or in the form of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), which is considered an indicator of the occurrence and development of obesity and adiposity. The immune system can also be associated with exacerbation of the disease and increased risk of death in patients with COVID-19 [5,8,10,16,17]. SAT is relatively slow, while VAT is a metabolically more active tissue that secretes inflammatory cytokines [9]. VAT is associated with metabolic syndrome, cardiovascular disorders, and increased susceptibility to infection and sepsis [18]. Hence, analysis of the relationship between fat levels Visceral and severity of infection with COVID-19 is very interesting. VAT and SAT can be rapidly and accurately measured and classified using magnetic resonance imaging or computed tomography (CT) [19]. The objective of this study is to examine the correlation between VAT and SAT fat and the severity and outcome of COVID-19 in hospitalized patients.

Methods and Material

Study design

The study design employed in this research is a cross-sectional descriptive approach. The study population consisted of medical records of individuals aged 18 years and above, who were diagnosed with Covid-19 using established diagnostic criteria such as clinical symptoms, lung CT findings, and a positive polymerase chain reaction (PCR) test for coronavirus. These patients were admitted to the hospital and underwent evaluation for the extent of lung involvement as well as measurements of visceral fat and subcutaneous fat using lung CT scans.

Sample selection

At first, by referring to the file of hospitalized patients, background information including gender and age of the people was collected. Then, by examining the results of lung CT, in addition to determining the percentage of lung involvement, the amounts of visceral fat and subcutaneous fat at the level of the upper pole of the kidney and below the costophrenic angle were determined. According to the criteria approved by radiology, we divided the severity of lung involvement into three categories: less than 50% as weak, between 50-75% as moderate, and above 75% as severe [20].

The method of performing subcutaneous and visceral fat work using the OsiriX system:

In the CT scan images from the OsiriX software, in the range of interest (ROI) menu, select the growing region (2D.3D) option, then select the 2D (two-dimensional) option, and then set the upper and lower thresholds according to the fat density and enter the numbers 50 and 150 respectively.

Then, we selected the desired area including subcutaneous or visceral fat at the level of the upper bridge of the kidney and below the costophrenic level, and we selected 1 point in it, and if it corresponds to the area of subcutaneous and visceral fat, the same area was displayed in green color. Otherwise, we chose

another point and checked the area selected by the software to see if it matched or not.

We continued this process until the end of the desired result, in which the density of the areas near the selected point was displayed in green color and the fat area of that area was shown as a number. Also, the ratio of visceral fat to SAT was determined. Then, by reviewing the patients' files, admission to ICU as well as the deaths of the patients were investigated and recorded. Finally, the relationship between the measured indicators and disease outcomes was investigated.

Patients who had the criteria for admission to ICU included oxygen saturation drop, ventilator dependence, progressive pulmonary involvement, and the need for intensive care.

Exclusion criteria for this study included patients under 18 years old, referral patients who were admitted more than 14 days after the onset of symptoms, patients without available CT scans for assessing lung involvement and measuring VAT and SAT, pregnant individuals, and patients with various malignancies.

Statistical analysis

The collected data were analyzed using the commercial statistical software SPSS-16. Descriptive statistics, such as frequency tables for qualitative variables and mean and standard deviation for quantitative variables were calculated. Additionally, relevant charts were generated to visualize the data. To examine the relationship between variables and disease severity, independent t-tests or ANOVA tests were employed. Furthermore, t-tests were utilized to compare means between different groups.

The study and all experimental protocols were approved by the Professional Ethics Committee of the Golestan University of Medical Sciences with the ethical code of IR.GOUMS.REC.1401.468. The informed consent was also obtained from all patients for the implementation of this project. All methods were carried out by relevant guidelines and regulations.

Results

This retrospective descriptive cross-sectional study included a total of 318 hospitalized Covid-19 patients. The mean age of the patients was 55.82 ± 15.39 and the mean number of days in the hospital was 11 ± 10.027. The demographic characteristics of the patients are provided in (Table 1).

Variables	Min	Max	Mean ± Standard deviation
Age (years)	18	96	55.82 ± 15.32
Duration of hospitalization (days)	1	74	11.25 ± 10.02
Visceral fat	5	475	143.69 ± 80.46
Subcutaneous fat	5	294.30	103.23 ± 49.55
Visceral to subcutaneous fat ratio	0.01	4.11	0.893 ± 0.599

Table 1: The demographic characteristics of the patients.

Out of all the individuals investigated, 161 people (50.6%) were women. Based on the information obtained from the study of Palaiodimos [10], and the study of Petersen et al. [21], we first divided the age into two categories, less than 50 years and more than 50 years, and then performed an analysis. The results showed that 206 patients (64.78%) were over 50 years old (Table 2).

Variables		Abundance (percentage)
Gender	Female	161 (50.6)
	Male	157 (49.4)
Age (year)	50 ≥	206 (64.78)
	50<	109 (34.27)

Table 2: Patients' abundance with Covid-19 hospitalized by gender and age.

The CT scans of patients with the lowest and highest amounts of VAT and SAT have also been depicted in (Figure 1-4). During the study period, the overall mortality rate was 23.9%. For individuals over 50 years old, the mortality rate was 32.5%, while it was 7.3% for those under 50 years old (Table 3).

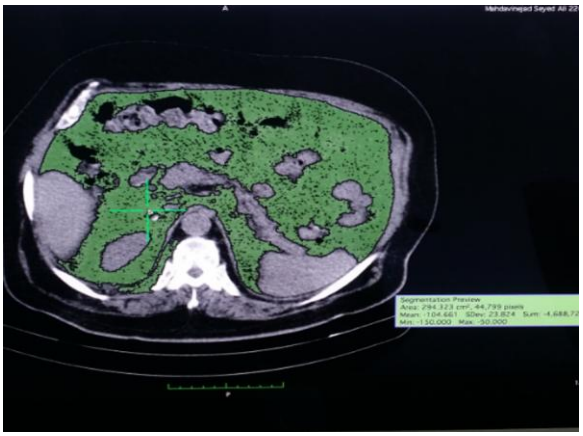

Figure 1: The CT scan of the patient showing the highest amount of visceral fat.

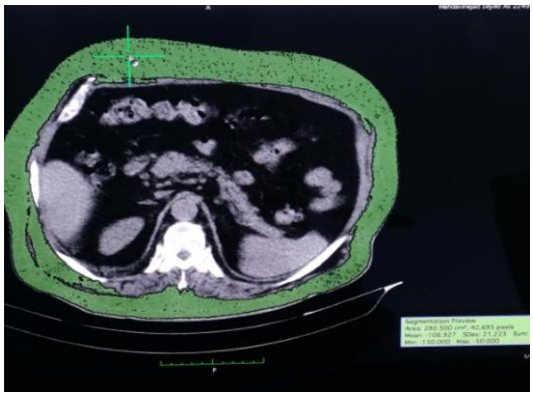

Figure 2: The CT scan of the patient showing the lowest amount of visceral fat.

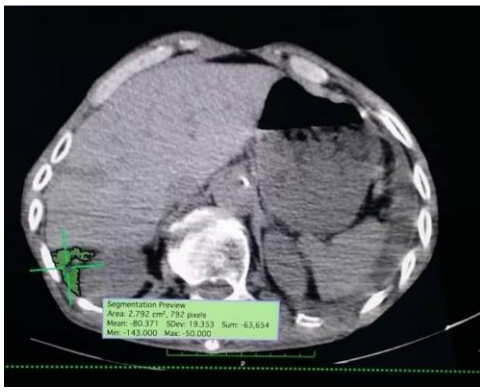

Figure 3: The CT scan of the patient showing the highest amount of subcutaneous fat.

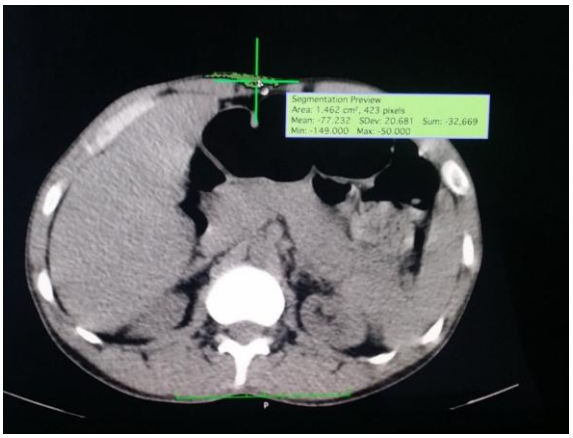

Figure 4: The CT scan of the patient showed the lowest amount of subcutaneous fat.

Variable		Outcome	Number of patients (percentage)
Age	50 ≥	Recovery	138 (66.03)
		Death	68 (67.47)
	50<	Recovery	101 (92.66)
		Death	8 (7.34)

Table 3: The relationship between age and the outcome of hospitalized patients with Covid-19.

The results of the independent t-test showed a significant relationship between visceral and SAT and the ratio of VAT to SAT with gender. The mean visceral fat of men (117.55 ± 51.56) was higher than that of women, while the mean SAT of women (175.93 ± 79.79) was higher than that of men. Consequently, the ratio of VAT to SAT was higher in men (1.23 ± 0.61) (Table 4).

Variables		Visceral fat		Subcutaneous fat		Visceral to subcutaneous fat ratio	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Gender	Male	117.55	± 51.56	110.63	± 66.74	1.23	± 0.61
	Female	89.26	± 43.31	175.93	± 79.79	0.56	± 0.35

P-value		0.006		0.005		0.001	
Age (years)	≤50	94.35	± 49.27	134.35	± 78.63	0.8896	± 0.65
	50<	107.86	49.19	148.35	± 81.19	0.8957	± 0.57
P-value		0.021		0.153		0.93	
Duration of hospitalization (days)	7≤	96.92	± 48.44	132.67	± 72.19	0.892	±0.60
	7>	109.48	± 49.9	153.47	± 86.50	0.9028	± 0.60
P-value		0.025		0.022		0.875	
Severity of lung involvement (percentage)	≤50	101.32	±53.04	134.15	± 80.6	0.95	±0.65
	50-75	104.48	± 46.61	152.35	± 82.07	0.84	±0.56
	≥75	107.29	± 43.6	157.2	71.76	0.79	±0.43
P-value		0.749		0.093		0.163	
Need for ICU admission	Yes	110.49	± 51.94	142.75	± 70.64	0.8897	± 0.5
	No	101.4	± 48.73	144.76	± 83.15	0.8909	± 0.63
P-value		0.17		0.852		0.98	
Recovery/death	Recovery	102.57	± 49.98	143.74	± 81.81	0.9067	± 0.62
	Death	106.32	± 48.75	141.69	± 73.95	0.8579	± 0.52
P-value		0.567		0.846		0.498	

Table 4: The relationship between visceral and subcutaneous fat and the ratio of visceral to subcutaneous fat in patients with COVID-19 and gender, age, duration of hospitalization, severity of lung involvement, need for ICU admission, and recovery/death.

A significant relationship was observed between the amount of VAT and age, with the mean VAT in the age group over 50 years old being higher than that in the age group under 50 years old (p-value = 0.021). The mean SAT was also higher in the age group over 50, but no significant relationship between age and SAT was found (p-value = 0.153). Additionally, no significant relationship was found between the ratio of VAT to SAT and age (p-value = 0.93), but a significant relationship was found between the amount of VAT and age over 50 years (p-value = 0.021).

Next, the duration of hospitalization was divided into two categories, less than or equal to 7 days and more than 7 days, based on the median, and the relationship between fats and duration of hospitalization was investigated. The results showed a relationship between the duration of hospitalization and the amount of VAT and SAT, with respective p-values of 0.022 and 0.025.

Although the amount of visceral and SAT was higher in patients with more severe lung involvement, this difference was not statistically significant (p-value > 0.05). Similarly, the amount of VAT in individuals admitted to the ICU was higher than those not admitted, but this difference was not statistically significant (p-value = 0.17).

Furthermore, the relationship between fats and the occurrence of deaths was examined, but the results of the independent t-test did not show a significant association between the amount of fats and the occurrence of deaths (p-value > 0.5). The mean age of the participants was 57.22 years with a standard deviation of 16.02 years. Also, the mean thickness of epicardial fat was 4.57±1.97mm and retro-areolar fat was 19.5±9.81mm.

The normality of the data was evaluated by Anderson-Darling, D'Agostino-Pearson, Shapiro-Wilk, and Kolmogorov-Smirnov tests. Based on these tests, epicardial and retro-areolar fat did not follow the normal pattern. According to the Anderson-Darling and Kolmogorov-Smirnov tests, the patient's age followed the normal pattern, but according to the D'Agostino-Pearson and Shapiro-Wilk tests, it did not follow the normal logic.

The results of this study showed that the age of patients is associated with the mortality rate (r=0.21 and P<0.001), but not with admission to the ICU (r=0.08 and P=0.15). It was also shown that the age of patients has an inverse relationship with the prevalence of fatty liver (r = -0.17 and P <0.001) and retro-areolar fat (r = -0.16 and P <0.001) and a direct relationship with epicardial fat. (r=0.28 and P>0.001). While the age of the patients was not associated with the prevalence of gynecomastia. The results of the present study showed that bilateral gynecomastia is not associated with the prevalence of fatty liver and the amount of epicardial and retro-areolar fat. It also has no significant relationship with mortality or admission to the ICU.

However, right-sided gynecomastia was associated with the prevalence of fatty liver (r = -0.11 and P = 0.05), while it was not associated with mortality and admission to the ICU. On the other hand, left gynecomastia was associated with epicardial fat (r=0.14 and P=0.01), but was not associated with mortality and admission to the ICU.

According to the findings of this study, the prevalence of fatty liver was directly related to the amount of epicardial fat (r = 0.12, P = 0.02) and retro-areolar fat (r = 0.34, P < 0.001). However, there was no correlation between the prevalence of fatty liver and mortality or admission to the ICU. Eventually, the final results of the study showed that there is no relationship between mortality and admission to the ICU with the amount of epicardial or retro-areolar fat.

Discussion

The current study involved the analysis of medical records from 318 patients, who had a mean age of 55.82 ± 15.39 years and a gender ratio of 50.6%. The mean measurement of VAT was reported as 2103.23 cm.

In a study conducted by Hersh Chandarana et al. [9], the objective was to assess the estimation of VAT, SAT, and total adipose tissue (TAT) on abdominal CT scans in COVID-19 patients with varying degrees of severity. The study included 51 patients diagnosed with COVID-19, with a mean age of 60.8 years, and 80% of them were male. The mean measurement of VAT was reported as 240.6 cm^2.

Similarly, M. Watanabe et al. [22] investigated the impact of VAT on the severity of COVID-19 based on the interpretation of chest CT scans. The study involved 150 patients, with a mean age of 70.8 years and a gender ratio of 65.7% male. The mean measurement of VAT was reported as 173.4 cm^2, which was lower compared to our study. This discrepancy may be attributed to the higher mean age of the patients in their study.

In a study conducted by Guillaume Favre et al. [23] involving 165 patients, with a mean age of 65.8 years

and 81% males, it was observed that VAT accumulation provides better predictive value for the severity and outcome of COVID-19 compared to SAT and body mass index (BMI). The mean measurement of VAT in this study was reported as 131.7 cm^2.

Another study by L Yang et al. [4] aimed to investigate the relationship between fat tissue distribution and the severity of the clinical course in patients with severe acute respiratory syndrome caused by the coronavirus. The study included 45 patients, with a mean age of 66 years and a gender ratio of 70% male. The mean measurement of VAT in this study was reported as 103.4 cm^2.

A study conducted by Petersen et al. [21] aimed to explore the association between fat distribution and the severity of COVID-19 in a medical center in Berlin, Germany. The study included 30 patients, with a mean age of 65.6 years and a gender ratio of 60% male. The mean measurement of VAT was reported as 111.6 cm^2.

The findings from these studies indicate that the mean measurement of VAT varies according to the mean age and gender distribution of patients in different studies. In our study, the patients' weight and body mass index were not recorded in the medical records. Additionally, the mean measurement of SAT in our study was 143.69 cm^2. In comparison, Favre et al [23]. reported a mean measurement of SAT as 152.8 cm^2, Watanabe et al. [22] reported 155 cm^2, Yang et al. [4] reported 108.2 cm^2, Chandarana et al. [9] reported 179.6 cm^2, and Petersen et al. reported 90 cm^2. The mean measurement of SAT in our study aligns closely with the findings of other studies.

Furthermore, in our study, although the mean measurements of visceral and SAT increased with the severity of lung involvement, these differences were not statistically significant. Additionally, no significant differences were observed in the amount of fat between patients requiring intensive care unit (ICU) admission and those hospitalized in regular wards.

In the present study, the researchers examined the relationship between body mass index (BMI) and CT estimation of fat content in hospitalized patients with COVID-19. Chandarana et al [9] discovered that patients requiring hospitalization had higher VAT compared to outpatients (13). Similarly, Petersen et al. [21] found that an increase in visceral and abdominal fat tissue specifically increased the likelihood of COVID-19 severity [32]. Watanabe et al [2] also demonstrated that VAT tissue was associated with worse clinical outcomes in COVID-19 patients [22].

Furthermore, Favre et al. [23] observed that VAT had the best predictive value for severe COVID-19, independently of COVID-19 severity, while SAT was not related to disease severity [23]. A systematic review by Pranata et al [7]. supported these findings, showing that visceral obesity was associated with increased COVID-19 severity, whereas subcutaneous obesity was not [24].

Consistent with previous studies, our findings revealed a relationship between increased VAT tissue and prolonged hospitalization, more severe lung involvement, ICU admission, and mortality. However, these associations were not statistically significant. It is worth noting that all patients in our study were hospitalized due to the severity of the disease, which may explain the lack of significant differences. The

mortality rate in our study was approximately 23%, which aligns with the rates reported in other studies.

Petrilli et al. reported a mortality rate of 24% in their study of COVID-19 patients hospitalized in the United States [8] Giacomelli et al [5], investigated the risk of death in COVID-19 patients in Milan, Italy and found a mortality rate of approximately 20%. [5] Palaiodimos et al [10] studied 200 hospitalized patients with COVID-19 and reported a mortality rate of 24% [8].

In our study, we also observed a significant increase in mortality with advancing age, consistent with previous research. Giacomelli et al [5], Petrilli et al [8], and Palaiodimos et al [10]. all found that older age and comorbidities were associated with increased hospitalization and risk of death in COVID-19 patients.

Additionally, our study investigated the relationship between visceral and SAT and their ratio with age. We found that the amount of VAT increased in patients over 50 years old, while the amount of SAT decreased. These findings align with the study conducted by Scheffler et al [25], which showed that higher SAT area had a protective effect against mortality, even after adjusting for age, sex, and BMI. They also found associations between higher abdominal circumference, total fat level, SAT area, and worsening of COVID-19 pneumonia, with VAT demonstrating the strongest association.

Conclusion

In conclusion, according to the findings of this study involving hospitalized patients with Covid-19, age was found to have a significant association with disease severity and mortality rate. Additionally, the amount of VAT was found to be related to the duration of hospitalization. Although an increase in VAT and severity of lung involvement was observed to be associated with higher rates of ICU admission and mortality, these relationships did not reach statistical significance. Furthermore, individuals with higher levels of lung involvement tended to have higher amounts of SAT, but this relationship was not statistically significant. Notably, SAT levels were lower among individuals hospitalized in the intensive care unit, but this finding also did not reach statistical significance in terms of its association with mortality rate.

Consent for publication

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Ethical approval and consent to participate

The study and all experimental protocols were approved by the Professional Ethics Committee of the Golestan University of Medical Sciences with the ethical code of IR.GOUMS.REC.1401.468. The informed consent was also obtained from all patients for the implementation of this project. All methods were carried out by relevant guidelines and regulations.

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author but

restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available in the form of an Excel file from the authors upon reasonable request and with permission of Elahe Sadat Alavi.

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Author's contribution

- Elahe Sadat Alavi: Patients visiting and necessary data collection.
- Alireza Fatemi: Manuscript writing and Data entry.
- Somayeh Livani: Radiologic analysis and interpretation.
- Samira Eshghinia: Supervision

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