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A comparative analysis of COVID-19 deaths during the alpha and delta to Omicron transition, from a forensic perspective in Greece

Dimitrios Kouzos[1], Konstantinos Katsos[1], Ioannis Papoutsis[1], Artemisia Dona[1], Nikolaos Georgiadis[2], Theodoros Sergentanis[2], Chara Spiliopoulou[1] and Emmanouil Sakelliadis[1*]

Abstract

Background Autopsy is the method of choice for examining risk factors, concomitant diseases, and the evolution of pathology in COVID-19 decedents. The global transition from the Alpha and Delta variants (before December 2021) to the Omicron variant (after January 2022) raised questions about the demographic and pathologic characteristics of COVID-19-positive decedents who underwent autopsy.

A comparative retrospective analysis, including forensic autopsy data, was conducted to categorize cases by the dominance of the Delta and Omicron variants. The main variables examined included data like age, sex, place of death, vaccinations performed, alcohol and tobacco use, toxicological examination results, other pathology, several COVID-19 complications (e.g., diffuse alveolar damage, acute respiratory distress syndrome, microthrombosis), and histological examination results. A statistical analysis was performed to assess the differences between the two respective groups.

Results The deceased during the Omicron period were significantly older and had pre-existing cardiovascular conditions. The Omicron period was characterized by less fulminant respiratory pathology, as serious COVID-19-related complications (e.g., diffuse alveolar damage, microthrombosis) were less common than in the Delta period. Inpatient deaths were more common during the Omicron period. Other factors, such as alcohol and tobacco use, and different concomitant diseases, did not offer statistically significant results.

Conclusions Older median age and a higher burden of cardiovascular disease are indicated by the mortality patterns described in the Omicron period. Further research focusing on virological and histopathological data may aid in examining the trajectory of the COVID-19 mortality.

Keywords Forensic Medicine, Post-Mortem Examination, COVID-19, SARS-CoV-2, Delta, Omicron

*Correspondence:
Emmanouil Sakelliadis
esakelliadis@med.uoa.gr
[1]Department of Forensic Medicine and Toxicology, National and Kapodistrian University of Athens, Athens, Greece
[2]School of Public Health, Department of Public Health Policy, University of West Attica, Athens, Greece

Introduction

Several different clinical presentations and outcomes reveal the significance of autopsies in the cause of death investigation during the COVID-19 pandemic. The responses of public health systems worldwide, resource allocation, and clinical understanding of COVID-19 are among the most essential reasons for the need for high accuracy in documenting COVID-19 mortality patterns (Gill and DeJoseph 2020).

Autopsy is the most valuable examination for the determination of the cause of death (Hirschbuhl et al. 2020), as it clarifies most validly whether COVID-19 infection was the cause of death or it was an incidental event (Geller et al. 2022).

The fourth COVID-19 variant, also known as the Delta variant, was first detected in India in October 2020, and on April 4, 2021, it was designated a variant of interest. The Omicron variant followed it, designated a variant of concern on November 26, 2021 (Zhou et al. 2022). According to literature, the Delta variant wave ended in December 2021, and afterwards the Omicron variant wave commenced (Barton et al. 2020).

Studies from Greece report that the Alpha period lasted from weeks 2–26 of 2021, the Delta period lasted from weeks 27–51 of 2021, and the Omicron period commenced in week 51 of 2021 (Malli et al. 2023). Therefore, the identification of any possible fluctuation of variables of the causes of death of COVID-19 decedents who underwent autopsy is crucial for forensic and clinical practitioners as well.

Demographic factors appear to contribute to COVID-19 mortality rates (Kirillov et al. 2021; Mikhaleva et al. 2021). The age and gender of decedents from COVID-19 infection seem to be influential towards mortality rates, as the incidence is higher among males (Kirillov et al. 2021; Koirala et al. 2021; Sakelliadis et al. 2020), while older individuals were affected more often (Sakelliadis et al. 2020; Gunawardena et al. 2021; Menezes et al. 2022). Other demographic factors, such as nationality, are usually limited in many reports, as analyses include only local data in the respective countries (Koirala et al. 2021; Sakelliadis et al. 2020). Socioeconomic status appears to affect the mortality rates indirectly during the COVID-19 era, as suicide rates were affected because of COVID-19-related socioeconomic burdens in some cases (Koirala et al. 2021; Calati et al. 2021).

Another critical aspect of COVID-19-related mortality is the examination of the place of death. Many patients seem to succumb during an inpatient setting, commonly after remaining in an intensive care unit for a significant period (Mikhaleva et al. 2021; Gunawardena et al. 2021). In contrast, others have been reported to deteriorate and die in a domestic setting rapidly. However, there have been reports of patients developing a combination of viral and bacterial infections during hospital admission (Fabbri et al. 2022), resulting from hospital-acquired pathogens.

COVID-19 mortality has been related to multi-organ pathology (Gonzalez Pessolani et al. 2021; Jonigk et al. 2022; Kaur and Kaur 2022) and has been proven to interact with pre-existing diseases (Kirillov et al. 2021; Hanson et al. 2022). Furthermore, there has been a documented shift in COVID-19 mortality patterns across consecutive waves of the pandemic (Danics et al. 2021).

The literature constantly cites cardiovascular diseases such as hypertension, diabetes mellitus, obesity, and other health conditions as risk factors that increase the possibility of severe illness and death by COVID-19 (Jonigk et al. 2022; Danics et al. 2021). At the same time, several serious complications are often present (diffuse alveolar damage, acute respiratory distress syndrome, microthrombosis).

Furthermore, multiple systems are influenced by COVID-19 infections, underscoring the virus's broad pathogenicity. Myocyte hypertrophy and myocardial inflammatory infiltrates, liver congestion, lobular necrosis, steatosis, and occasional portal microthrombi, acute tubular necrosis (ATN), focal glomerular capillary thrombi, occasional tubular epithelial vacuolization, and other systemic conditions are among the most common histopathological findings following an autopsy in COVID-19-related deaths (Menezes et al. 2022; Gonzalez Pessolani et al. 2021; Malik et al. 2021).

Obesity appears to be a major risk factor when it comes to COVID-19 mortality, as the decedents of multiple studies tend to be prone to it (Kirillov et al. 2021; Danics et al. 2021).

The vaccination status of COVID-19 patients adds another layer of complexity to the issue of mortality caused by the infection. Since the COVID-19 pandemic began, several vaccines have been developed by various producers. According to the literature, these vaccines are quite efficient against the Alpha variant, but only intermediate efficiency against Gamma and Delta variants, and somewhat ineffective against the Beta and Omicron variants (Zhou et al. 2022; Hadj Hassine 2022). However, several complications (myocarditis, thrombosis, etc.) have been reported after the vaccination of the population, as some vaccines seem to be more effective but less safe than others (Li et al. 2022). Especially, thrombosis seems to be one of the most severe and atypical adverse effects of the COVID-19 vaccination, along with anaphylaxis, fever, joint and muscular pain, headache, weakness, nausea, chills, erythema, lymphadenopathies, and other manifestations that have also been described (Bilotta et al. 2021).

It is accepted, however, that mass vaccination reduces the severity of COVID-19 symptoms and mortality.

Therefore, autopsy findings may differ between vaccinated and unvaccinated individuals, while the emergence of new variants renders several vaccines obsolete.

The value of toxicological examinations (De-Giorgio et al. 2021) in the death investigation procedure is highlighted, as it provides valuable information in cases where an external factor is the cause of death (Malik et al. 2021). The results of toxicological examination demonstrate whether any drugs, alcohol, or other substances were involved in the outcome of death. Several studies describe cases where the toxicology examination revealed poisoning as the real cause of death (Malik et al. 2021; De-Giorgio et al. 2021), while the individuals were COVID-19 positive. In cases like these, the COVID-19 positivity was misleading in the cause of death investigation. The need for differentiation between dying "with" and ''from" COVID-19 (De-Giorgio et al. 2021) is manifested via such examples.

Concerning autopsy findings in decedents during the Delta wave, the lungs were purple, with increased consistency on palpation and absent crepitus. Histopathological examinations often revealed acute pulmonary edema (70%) and diffuse alveolar damage at different stages (Jeican et al. 2023). However, a significant shift emerged in autopsy results during the consequent Omicron wave of the COVID-19 pandemic. Typical histopathological findings on microscopic examination were still detected, unrelated to the causative variant, but were significantly less common (50% versus 80–100%) and less severe in cases infected with omicron variants than in cases infected with previous variants ($p < 0.05$). Therefore, COVID-19 infection ceased being the leading cause of death during this wave (Schwab et al. 2023).

The transmissibility of the COVID-19 virus increased after the emergence of the Omicron variant, while its virulence decreased (Holmes 2024), thereby affecting the cause-of-death percentages. A 13-fold increase in viral transmissibility of the Omicron variant has been reported in the literature, compared to the Delta and Alpha variants (Shamabadi and Akhondzadeh 2022).

According to a study, the Delta variant produced the highest daily case numbers and the highest weekly hospitalization rate. The Omicron variant produced the second-highest daily case number, but the weekly hospitalization rate was the lowest of all the waves (Brussow 2022).

The total number of COVID-19 cases recorded in Greece by the end of the Alpha and Delta period (December 2021) was 1.210.853 and continued to rise sharply to 3.676.502 by the middle of 2022, when the Omicron variant was dominant. This demonstrates the high virulence of the Omicron variant, which led to widespread infection during the first months of 2022. Additionally, 4,5% of the total cases in the middle of 2022 were due to reinfections caused by the new variant (Organization 2021, 2022).

Deaths from COVID-19 pneumonia became scarcer, as the Omicron variant did not affect the lower respiratory system (Day and G.S., Lion S, Otto SP., 2020). In contrast, a potential rise in sudden deaths at a domestic setting, due to concomitant disease, was suggested, as most decedents died ''with" rather than ''of" COVID-19 infections during the Omicron wave(Friis, et al. 2020). In Greece, mortality due to COVID-19 infection also varied between the two periods. By the end of the Alpha and Delta periods, 20.790 deaths had been documented, and this number increased to 30.232 by the middle of 2022 (Organization 2021, 2022). This increase is not comparable to the significant rise in COVID-19 cases during the Omicron variant's dominance period.

Meanwhile, deaths, intensive care unit (ICU) admissions, and hospitalizations manifested a decreasing trend worldwide (Ward et al. 2022; Wolter et al. 2022; Nyberg et al. 2022). However, COVID-19 infections still maintain their mortality potential as they can still cause severe disease and be lethal, especially in unvaccinated patients (Johnson 2021). In Greece, ICU hospitalizations decreased vastly, from 627 at the end of 2021 to 97 in the middle of 2022. This fact demonstrates a significant decompression of the health system during the Omicron period (Organization 2021, 2022).

Therefore, the Omicron period is a distinct recessive phase of the COVID-19 pandemic and should be addressed separately from the other phases.

Methods

For this retrospective study, the authors reviewed data from forensic autopsies performed at the Department of Forensic Medicine and Toxicology. More specifically, cases examined from the beginning of the pandemic to December 31 st, 2023, all involving deaths that occurred while a positive PCR or Rapid test for COVID-19 was reported. In total, 116 case records were included. There was no other input included in the study, from any other Forensic Department in Greece or Statistical Centers, in the form of raw data or statistically examined percentages.

Autopsy-derived data from cases of death in the periods before and after the Delta-to-Omega shift comprise the present study, as suggested by the literature.

It focuses on:

- demographic factors such as the age, gender, and nationality of the decedents,
- the place where the death took place (home or hospital),
- diagnosed with serious COVID-19 complications (histological findings of severe COVID-19

complications such as diffuse alveolar damage or acute respiratory distress syndrome), as well as potentially fatal COVID-related complications such as pulmonary embolism,
- correlation with factors like tobacco use, excessive alcohol intake, body weight, vaccination status,
- toxicological examination results,
- concomitant diseases and
- histopathological findings.

The study aims to examine the variables set by the authors before and after the Omicron period of the COVID-19 pandemic, to assess possible differences between the Omicron and the previous periods.

Statistical analysis

Statistical analysis was performed with STATA/SE version 16 (Stata Corp., College Station, TX, USA). Statistical significance was defined as a 2-sided *P* value of < 0.05.

For every variable, descriptive statistics were provided. Interquartile ranges (IQR) and medians were used to describe continuous non-parametric variables. Numbers and percentages were used to represent categorical variables. For comparing continuous and categorical data, the Mann–Whitney U test and the Pearson chi-square test were employed, respectively. When the Pearson chi-square test was deemed unsuitable due to the comparatively small sample size, Fisher's exact test was used instead.

The text was edited for grammar and language with Grammarly (Grammarly Inc., San Francisco, CA). The authors reviewed and edited the content for accuracy and take full responsibility for the final manuscript.

Results

A summary of the results is illustrated in Table 1.

A total of 116 cases were included in our study, comprising 28 from the Alpha and Delta periods and 88 from the Omicron period. Forty-two of the individuals succumbed from COVID-19 related pneumonia (7 cases in Alpha and Delta period vs 35 cases in Omicron period, 6, 03% vs 30,17%), 18 individuals succumbed from serious COVID-19 infection complications (11 cases in Apha and Delta vs 7 cases in Omicron, 9,48% vs 6,03%), 34 of them from cardiovascular causes (2 instances in Alpha and Delta period vs 32 cases in Omicron period, 1,72% vs 27,58%) and 22 of them from other reasons like trauma, poisoning, malignancy, other pathological conditions (8 cases in Alpha and Delta period vs 14 cases in Omicron period, 6,89% vs 12,06%).

In the Alpha and Delta period, most decedents were male (53.57%) of Greek origin (92.86%), with a median age of 68.5 years (IQR: 54–77). During the Omicron period, most cases were male (65.91%) of Greek origin (89.77%), with a median age of 77.5 years (IQR: 63.5–88). A significant age difference was found between the two periods ($p = 0.013$), but no significant differences were found in gender or nationality ($p = 0.239$ and $p = 1.000$, respectively).

Statistically significant differences were noted in the place of death and the presence of serious COVID-related complications between the two periods. A significantly higher percentage of deaths occurred at home during the Alpha and Delta period (14.29%) compared to the Omicron period (1.14%) (Fisher's exact test, $p = 0.012$). Additionally, serious COVID-related complications were significantly more common in the Alpha and Delta period (45.83%) compared to the Omicron period (14.26%) ($p = 0.003$).

There were no statistically significant differences between the two periods in terms of alcohol use, smoking, increased body weight, and vaccination status for COVID-19. There were no cases where alcohol use was documented during the Alpha and Delta period, while it was noted in 15.85% of cases during the Omicron period (Fisher's exact test, $p = 0.060$). Smoking was reported in 15% of cases during the Alpha and Delta period and 32.93% during the Omicron period ($p = 0.171$). Increased body weight was observed in 25% of cases during the Alpha and Delta period and 34.09% during the Omicron period ($p = 0.486$). Vaccination rates were 63.64% during the Alpha and Delta period and 76.06% during the Omicron period ($p = 0.460$). Positive toxicology results for central nervous system (CNS) acting drugs and illegal substances showed no significant difference between the two periods, with 21.43% positive during the Alpha and Delta period and 13.64% positive during the Omicron period ($p = 0.371$).

In terms of concomitant diseases, cardiovascular diseases were significantly more prevalent during the Omicron period (82.95%) compared to the Alpha and Delta period (44.44%) ($p < 0.001$). However, no significant differences were found for metabolic diseases (29.63% in Alpha and Delta vs. 31.4% in Omicron, $p = 0.863$), malignancies (22.22% in Alpha and Delta vs. 13.79% in Omicron, $p = 0.294$), mobility issues (7.41% in Alpha and Delta vs. 20.93% in Omicron, Fisher's exact test, $p = 0.150$), and psychiatric conditions (18.52% in Alpha and Delta vs. 12.79% in Omicron, $p = 0.456$).

Regarding histological findings, there were no significant differences between the two periods in the type of infection. Viral-only infections were observed in 63.64% of cases during the Alpha and Delta period and 60% during the Omicron period ($p = 0.790$). Bacterial infections, with or without viral infections, were present in 36.36% of cases during the Alpha and Delta period and 40% during the Omicron period. Similarly, inflammatory infiltration of other organs, such as the kidneys and liver, did not

Table 1 Summary of results

Case Characteristics		**Alpha and Delta Period**	**Omicron Period**	***p*-value**
Autopsies Performed		**28**	**88**	
Age Median (IQR)		68.5 (54–77)	77.5 (63.5–88)	0.013
Basic Demographics				
Gender N (%)	Male	15 (53.57%)	58 (65.91%)	0.239
	Female	13 (46.43%)	30 (34.9%)	
Nationality N (%)	Greek	26 (92.86%)	79 (89.77%)	Fisher's 1.000
	Other	2 (7.14%)	9 (10.23%)	
Place of Death	Hospital	24 (85.71%)	87 (98.86%)	Fisher's 0.012
	Home	4 (14.29%)	1 (1.14%)	
Medical History/Clinical Information				
History of alcohol use	Yes	0 (0%)	13 (15.85%)	Fisher's 0.06
	No	21 (100%)	69 (84.15%)	
History of Smoking	Yes	3 (15%)	27 (32.93%)	0.171
	No (or stopped > 10 years ago)	17 (85%)	55 (67.07%)	
Weight	Increased	7 (25%)	30 (34.09%)	0.486
	Normal	21 (75%)	58 (65.91%)	
COVID-19 Vaccination Status	Vaccinated	7 (63.64%)	54 (76.06%)	0.460
	Unvaccinated	4 (36.36%)	17 (23.94%)	
Serious COVID-19 Related Complications	Yes	11 (45.83%)	7 (14.26%)	0.003
	No	13 (54.17%)	42 (85.71%)	
Concomitant Diseases				
Cardiovascular	Yes	12 (44.44%)	73 (82.95%)	< 0.001
	No	15 (55.56%)	15 (17.05%)	
Metabolic	Yes	8 (29.63%)	27 (31.4%)	0.863
	No	19 (70.37%)	59 (68.6%)	
Malignancy	Yes	6 (22.22%)	12 (13.79%)	0.294
	No	21 (77.78%)	75 (86.21%)	
Mobility	Yes	2 (7.41%)	18 (20.93%)	Fisher's 0.150
	No	25 (92.59%)	68 (79.07%)	
Psychiatric	Yes	5 (18.52%)	11 (12.79%)	0.456
	No	22 (81.48%)	75 (87.21%)	
Histopathological Examination Findings				
Type of infection	Viral only	14 (63.64%)	18 (60%)	0.79
	Bacterial infection (with or without viral)	8 (36.36%)	12 (40%)	
Inflammatory infiltration of other organs (kidneys, liver, others)	Yes	6 (27.27%)	10 (29.41%)	0.863
	No	16 (72.73%)	24 (70.59%)	
Toxicological Examination Findings				
Toxicology Results (CNS drugs)	Positive	6 (21.43%)	12 (13.64%)	0.371
	Negative	22 (78.57%)	76 (86.36%)	

show significant differences between the periods, with 27.27% in the Alpha and Delta period and 29.41% in the Omicron period ($p = 0.863$).

Discussion

The results of our study highlight several statistically significant differences between the two periods of the COVID-19 pandemic examined. The most notable results regard the age of the decedents, the place of death, the incidence of serious complications of COVID-19 infections, and the frequency of cardiovascular disease among them. In summary, a shift towards older decedents was observed during the Omicron period of the COVID-19 pandemic, along with a lower incidence of serious COVID-19 complications and a significantly higher rate of pre-existing cardiovascular disease. Furthermore, most decedents' deaths occurred in the hospital, unlike earlier periods of the pandemic. Other variables like the use of tobacco, excessive alcohol intake, different diseases, obesity, and others still provide context of value despite not reaching a statistically significant result.

Age differences

At the end of the Alpha and Delta period, in Greece, most decedents were older than 65 years (82.7%), while 16.5% were between 40 and 64 years old. Lower mortality rates characterized younger ages. During the Omicron period, the percentage of decedents aged 65 and older increased to 84.1%, while those aged 40–64 accounted for 15.2% of total deaths. Younger individuals were not significantly affected by COVID-19-related mortality (Organization 2021, 2022).

According to our results, the median age of the deceased COVID-19-positive individuals who underwent autopsy increased significantly during the Omicron period, to 77.5 years (IQR: 63.5–88), compared with 68.5 years (IQR: 54–77) during the Delta period ($p = 0.013$). Several epidemiological factors need to be considered to interpret these results.

First, the vaccination status of the population was altered drastically during the two periods. Almost 8 million vaccinations had been administered to the Greek population by July 2022 (Malli et al. 2023), and vaccinations continued at a rapid pace. Thus, the Omicron period emerged in a population that was vaccinated mainly against COVID-19. It is known that most vaccines reduce the number of patients who develop COVID-19 symptoms, and some even reduce the risk of severe or critical disease (Grana, et al. 2022). The vaccinated population also manifests lower mortality rates against all COVID-19 variants (Johnson 2021). Therefore, vaccination is expected to prevent a relatively large number of people from dying from COVID-19 during the Omicron period, when most vaccinations were completed. Only older and frail individuals were at risk of the virus's lethal potential during the Omicron period.

However, mass vaccination of the population has led to the discovery of vaccine-induced thrombotic thrombocytopenia (VITT), characterized by a procoagulant state that can lead to venous or arterial thrombosis. According to estimates, this phenomenon affects approximately 1 in 100,000 to 1 in 1,000,000 individuals who received the adenoviral vector vaccine (Bilotta et al. 2021). It is obvious, then, that this possible complication of vaccination against COVID has been relatively rare and does not cause significant alterations to the mortality trends of COVID-19 in either period.

Furthermore, as the older population faces more concomitant diseases, it is expected that they will be prone to increased mortality rates after COVID-19 infection. Concomitant diseases make patients more vulnerable to severe outcomes from COVID-19 by affecting immune responses and causing severe illness and mortality (Bigdelou et al. 2022).

It is also known that the Omicron variant of the COVID-19 virus is characterized by increased transmissibility (Holmes 2024; Shamabadi and Akhondzadeh 2022). Consequent to this elevation was the formation of the second-highest peak of daily COVID-19 patients. During that period, it became increasingly complex to avoid contracting the virus, leading to large numbers of people, including older individuals, becoming infected.

Place of death

The place of death was another factor that differed in a statistically significant manner between the early (Alpha and Delta) and the Omicron period (Fisher's = 0.012). Specifically, 14.29% of Alpha and Delta period deaths occurred in a domestic setting, whereas the corresponding figure during the Omicron period was only 1.14%.

The interpretation of this result leads to consideration of individuals' fear during the primary stages of the COVID-19 pandemic, namely the Alpha and Delta periods. Since the outbreak of the COVID-19 pandemic, local governments have implemented several measures to reduce transmission of the virus. Social distancing, including spatial distancing of 2 m (Sakelliadis et al. 2020), along with generalized lockdowns (Iacobucci 2020), were the most prominent measures.

The measures instilled fear among those who had to face them, as the new disease seemed dangerous. Therefore, patients often delayed seeking medical care (Nakano et al. 2023; Lazzerini et al. 2020), trying to avoid being in a hospital setting that seemed infectious. The result of this delay was usually death in a domestic setting, during the Alpha and Delta period, as the patients did not manage to seek medical help on time.

Additionally, as mentioned earlier, the Omicron variant was responsible for the second-highest daily peak in COVID-19 patients. Such large numbers of patients with Omicron infections can be overwhelming and can overload the healthcare system. The intensive care unit can become inaccessible, and emergency services can become inadequate due to excessive demand (Kim et al. 2023). The result of this condition may be an increased number of inpatients who do not receive proper care and succumb during their hospitalization.

Serious COVID-19–related complications

Another rather notable finding was the abrupt decrease in serious COVID-19-related complications during the Omicron period compared with the Alpha and Delta periods (45,83% vs 14,26%, $p = 0{,}003$). Diffuse alveolar damage, acute respiratory distress syndrome, and thromboembolism were among the most prominent ones.

COVID-19 infection is often accompanied by some quite serious complications, which are usually related to fatal outcomes. The predominant lesion diagnosed by autopsy in severe and fatal COVID-19 infections is

diffuse alveolar damage in the lungs (Kaur and Kaur 2022). The formation of a hyaline membrane, alveolar epithelial cell hyperplasia, and interstitial inflammation characterizes it. Other common findings included microthrombosis, microangiopathy, and fibrinoid necrosis of small vessels (Mikhaleva et al. 2021; Peiris et al. 2021).

Earlier autopsy studies have shown that diffuse alveolar damage was typical in the early stages of COVID-19 (Alpha and Delta) (Kirillov et al. 2021; Mikhaleva et al. 2021; Menezes et al. 2022), often accompanied by microthrombi. Our results are consistent with prior literature and indicate a significant reduction in these complications during the Omicron wave.

The Omicron variant demonstrated increased transmissibility but decreased virulence. Deaths, ICU admissions, and hospitalizations decreased during the Omicron period (Ward et al. 2022; Wolter et al. 2022; Nyberg et al. 2022), as it caused less frequent lower respiratory tract pathology than the former waves and therefore reduced pulmonary damage.

Finally, the vaccination campaigns were mostly completed during the Omicron period, and their effect on the COVID-19 infections was more prominent, as they kept the severity quite limited (Grana, et al. 2022).

Cardiovascular disease prevalence

Cardiovascular diseases like hypertension, ischemic heart disease, and others, were more prevalent in decedents during the Omicron period than in decedents during the Alpha and Delta period (82.95% vs 44.44%; $p < 0.001$). These diseases contribute significantly to the development of severe disease after COVID-19 infection and even death (Jonigk et al. 2022; Danics et al. 2021).

The interpretation of the results of our study suggests that individuals with cardiovascular disease succumbed more often when they were infected with COVID-19 during the Omicron period than during the Alpha and Delta periods.

This finding is probably related to the increased median age of the COVID-19 infected decedents during the Omicron period, as it is also derived from the results of our study. The older population often faces concomitant diseases, and cardiovascular conditions are the leading cause of morbidity and mortality worldwide (Li et al. 2023).

Also, the severity of pulmonary complications during the primary waves of the COVID-19 pandemic (Alpha and Delta periods), as mentioned earlier, rendered the infections more lethal than during the Omicron period. Because of this fact, many individuals with cardiovascular diseases succumbed earlier and did not survive until the Omicron period, when the outcome of their death ensued.

Other findings and expanded observations

Alcohol abuse is known to compromise the human immune system, making these individuals more prone to respiratory infections (Nelson et al. 2008). Even though there was no statistically significant difference in alcohol consumption between the Alpha and Delta and Omicron periods of the COVID-19 pandemic, alcohol consumption rose to 15.85% during the Omicron period from 0% during the Alpha and Delta periods. This difference did not reach statistical significance, but it likely reflects behavioral factors that evolved over the course of the pandemic. A viable explanation would be that alcohol consumption can be a coping mechanism during the period of uncertainty and social isolation of the pandemic. A similar rise in tobacco use (15% to almost 33%) was observed between the two periods, but it also did not reach statistical significance.

Alcohol, tobacco, or nicotine consumption in the COVID-19 era has been studied, and it has been proven that alcohol consumption was used to relieve stress symptoms due to the pandemic (Mengin et al. 2022). Moreover, complications from the respiratory system often derive from current or former smoking habits during COVID-19 infection (Gallus et al. 2023). Excessive alcohol consumption has also been reported to be a well-known risk factor for elevated mortality rates during a COVID-19 infection (Forsyth et al. 2022), as it predisposes towards acute respiratory distress syndrome. However, such data (smoking, excessive alcohol intake) remain under-reported in the literature.

Another factor that did not reach statistical significance was the decedents' weight, which was defined as increased vs. normal in our study. The main ways it affects COVID-19 patients are the adiposity-related systemic inflammation and hyperactivation of the renin–angiotensin–aldosterone system (Leeuw et al. 2021). In contrast, the diagnosis and care of obese patients are often complicated by excess weight and ventilation difficulties (Gammone and D'Orazio 2021).

Obesity has been, however, related to severe COVID-19 diseases and mortality, and according to our results, a notable number of decedents were of increased weight, especially during the Omicron period. Diagnosis and medical care of overweight patients are often complicated.(Leeuw et al. 2021; Gammone and D'Orazio 2021).

The vaccination status of individuals included in the examined sample did not show a statistically significant difference (76,06% in Omicron vs 63,64% in Delta, p = 0,460). This result suggests that vaccination did not affect the autopsy sample, even though it seems to have affected overall mortality. At the end of 2021, 86.28% of intubated patients in the ICU in Greece were not or partially vaccinated, while in the middle of 2022, the respective percentage was reduced to 41.24% (Organization

2021, 2022). This shift demonstrates the success of the vaccination campaign in Greece, which led to mass vaccination and the partial effectiveness of the vaccines against the Omicron Variant (Zhou et al. 2022; Hadj Hassine 2022). One should keep in mind that vaccinated individuals may still succumb to COVID-19 infections (Johnson 2021).

Other types of chronic conditions, like malignancy (22.22% in Delta vs. 13.79% in Omicron) and psychiatric disease (22.22% in Delta vs. 13.79% in Omicron), produced an epidemiological mixture when examined in our sample. The outcomes of COVID-19 infections are similar to those of patients who are malignancy-free (Brar et al. 2020), so the mortality rates of patients with malignancies should follow the general population mortality rates and decrease during the Omicron period. Meanwhile, patients with psychiatric disease are often known to refuse to comply with their medications (Katz et al. 2019). This renders the outcomes of such patients' disease quite unpredictable. It seems that comorbidities can manifest at similar rates, despite different periods.

Toxicological screening for CNS-acting drugs and illegal substances was positive in about 1/5 of cases during the Alpha and Delta period and in about 1/8 of cases during the Omicron period. Patients with this specific profile seem unaffected by the different COVID-19 periods.

It is crucial to declare that the lack of statistical significance of certain results does not render them as useless. Building health status for specific patient profiles and applying it in smaller cohorts may still yield value from the results. In either way, future research through larger-scale analyses may evaluate these results differently and provide further results on the subject.

The aftermath of the COVID-19 pandemic should be an opportunity to learn from all the lessons to improve future public health. All the infrastructure and technological advancements established during the pandemic must be incorporated as standard public health measures, along with budgetary, planning, and delivery allocations by the Governments. Outbreak monitoring systems, along with Telemedicine options, need to be further implemented as standard medical practice, while academic, pharmacological, and technological advancements need to be prioritized (Mathew 2023).

Conclusion

Concluding this study, it should be highlighted how the transition from the Alpha and Delta period to the Omicron period of the COVID-19 pandemic affected certain aspects about COVID-19 mortality, The advanced age and higher percentage of cardiovascular disease during the Omicron era, mark towards a demographic shift that occurred in this time, cause probably by the mass vaccination, adjustments of public health and reduced virulence of the Omicron variant. Severe complications were therefore reduced during the Omicron period but still posed a threat to vulnerable individuals. Other variables that did not yield statistically significant results in the statistical analysis, such as alcohol intake, tobacco use, other diseases, and increased weight, may be used in future research.

Limitations

Autopsies were avoided to protect medical staff during the early stages of the COVID-19 pandemic (Alpha and Delta periods) for a prolonged period. Therefore, the sample of these periods is limited in absolute numbers, and many patient cases are not included in the study.

Abbreviations

COVID-19	Coronavirus Disease 2019
ATN	Acute tubular necrosis
ICU	Intensive care unit
PCR	Polymerase chain reaction
IQR	Interquartile ranges
CNS	Central nervous system
VITT	Vaccine induced thrombotic thrombocytopenia

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Data availability

Data and material are available upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethics Committee of the School of Medicine, National and Kapodistrian University of Athens, Decision No 989/21–10-2024.

Consent for publication

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Competing interests

The authors declare no competing interests.

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