### D.2.1.5 Karahan 2020

## Karahan, 2020

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| **Bibliographic Reference** | Karahan, S.; Katkat, F.; Impact of Serum 25(OH) Vitamin D Level on Mortality in Patients with COVID-19 in Turkey; Journal of Nutrition, Health and Aging; 2020 |

**Study details**

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| **Study design** | Case-control study |
| **Trial registration (if reported)** | Not reported. |
| **Study start date** | 01-Apr-2020 |
| **Study end date** | 20-May-2020 |
| **COVID-19 prevalence at the time of the study** | Higher prevalence (e.g. during peak of first wave) |
| **Aim of the study** | To evaluate the association of vitamin D status with disease severity and mortality in patients with COVID-19. |
| **County/ Geographical location** | Istanbul, Turkey. |
| **Study setting** | Research and training hospital. |
| **Population description** | The population was made up of 149 COVID-19 patients who were admitted into the hospital with confirmed COVID-19. |
| **Inclusion criteria** | Adult admitted to Health Sciences University, Bagcilar Training and Research Hospital with COVID-19. |

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| **Exclusion criteria** | No vitamin D (25(OH)D) values.<br><br>Clinical presentation compatible with COVID-19 but who did not have a PCR-based test for SARS-CoV2.<br><br>Paediatric patients. |
| **Vitamin D status measurements** | Serum 25(OH) vitamin D levels were studied by electrochemiluminescence method. Patients were stratified into different groups according to their serum 25(OH) vitamin D levels. Serum 25(OH) vitamin D level >30 ng/mL was accepted as normal. Vitamin D insufficiency and deficiency were defined as serum 25(OH) vitamin D levels of 21-29 ng/mL and <20 ng/mL, respectively. |
| **Methods used to confirm COVID-19 infection** | PCR but specific method not mentioned.<br><br>Classification of the severity of COVID-19 was done using the Chinese Clinical Guideline for classification of COVID-19 severity. Patient symptoms, laboratory values, and results of imaging studies performed at admission are used to determine severity of COVID-19.<br><br>Mild symptoms: Mild clinical symptoms and normal lung on radiologic imaging.<br><br>Moderate disease: Fever and pulmonary symptoms along with pneumonia on radiologic imaging.<br><br>Severe disease: The presence of any of the following criteria: i) respiratory distress (≥ 30 breaths/min); ii) oxygen saturation ≤ 93% at rest; iii) PaO2/FiO2 ≤ 300 mmHg or chest imaging shows obvious lesion progression > 50% within 24-48 hours).<br><br>Critical disease: The presence of any of the following criteria: i) respiratory failure and need for mechanical ventilation; ii) shock; iii) other organ failures that requires ICU care.<br><br>Since patients with mild COVID-19 were not hospitalized according to the Turkish national guidelines, the study did not involve any patient with mild disease. The study combined severe and critical COVID-19 in a single group named “severe-critical disease”. Patients were stratified into either to moderate or critical-severe COVID-19 groups. |
| **Methods of data analysis** | This evidence table has included patients as they were classified in the study. Patients were classified as either moderate or severe/critical COVID-19, and then also classified as survived or deceased. The study compared patients in the moderate arm to the severe/critical arm; and then compared patients who survived and patients who died.<br><br>Descriptive statistics were presented for continuous variables as either mean +/-standard deviation or median-interquartile range and compared with Independent Samples t-test or Mann-Whitney U tests depending on the distribution type of the data. Categorical |

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| | variables were reported as numbers and percentages and compared between groups by chi-square/Fisher exact test depending on the distribution of the data. Normal distribution was checked with the Kolmogorov-Smirnov test.<br><br>To evaluate the bivariate correlation between the serum 25(OH) vitamin D level and inflammatory marker, Pearson's correlation was used. Univariate and multivariable logistic regression analyses were used to determine the independent associates of mortality. For all analyses, a p-value of <0.05 was considered significant.<br><br>SPSS 26.0 (IBM Corporation, NY, US) was used to perform all statistical analyses. |
| **Attrition/loss to follow-up** | No loss to follow-up. |
| **Source of funding** | No sources of funding declared. |
| **Study limitations (Author)** | As a retrospective analysis, confounders that can impact the mortality rate were not controlled.<br><br>The sample size is small. |
| **Study limitations (Reviewer)** | Due to the inclusion criteria, there was not a wide range of COVID-19 disease classifications as it omitted the mild cases. |

**Study arms**

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| **Moderate COVID-19 (N = 47)**<br><br>Participants who had moderate COVID-19 |
| **Severe-critical COVID-19 (N = 102)**<br><br>Participants who made severe or critical COVID-19 |
| **Survived (N = 80)**<br><br>Participants who survived |
| **Deceased (N = 69)**<br><br>Participants who died |

**Characteristics**

**Arm-level characteristics**

| | Moderate COVID-19 (N = 47) | Severe-critical COVID-19 (N = 102) | Survived (N = 80) | Deceased (N = 69) |
|---|---|---|---|---|
| **Age** | | | | |
| Mean/SD | 56.1 (15.2) | 67 (14.1) | 60 (15.1) | 67.7 (14.1) |
| **Gender**<br>Female | | | | |
| Sample Size | n = 24 ; % = 51.1 | n = 44 ; % = 43.1 | n = 40 ; % = 50 | n = 28 ; % = 40.6 |
| **Ethnicity** | | | | |
| Custom value | NA | NA | NA | NA |
| **Comorbidities** | | | | |
| **Coronary heart disease** | | | | |
| Sample Size | n = 3 ; % = 6.4 | n = 41 ; % = 40.2 | n = 13 ; % = 16.3 | n = 19 ; % = 27.5 |
| **Hypertension** | | | | |
| Sample Size | n = 15 ; % = 31.9 | n = 70 ; % = 68.6 | n = 41 ; % = 51.3 | n = 44 ; % = 63.8 |
| **Diabetes** | | | | |
| Sample Size | n = 12 ; % = 25.5 | n = 49 ; % = 48 | n = 25 ; % = 31.3 | n = 36 ; % = 52.2 |
| **COPD** | | | | |
| Sample Size | n = 4 ; % = 8.5 | n = 11 ; % = 10.8 | n = 8 ; % = 10 | n = 7 ; % = 10.1 |
| **Malignancy** | | | | |
| Sample Size | n = 6 ; % = 12.8 | n = 17 ; % = 16.7 | n = 9 ; % = 11.3 | n = 14 ; % = 20.3 |
| **Chronic kidney disease** | | | | |
| Sample Size | n = 2 ; % = 4.3 | n = 27 ; % = 26.5 | n = 9 ; % = 11.3 | n = 20 ; % = 29 |
| **Chronic atrial fibrillation** | | | | |
| Sample Size | n = 0 ; % = 0 | n = 15 ; % = 14.7 | n = 2 ; % = 2.5 | n = 13 ; % = 18.8 |
| **Congestive heart failure** | | | | |
| Sample Size | n = 0 ; % = 0 | n = 18 ; % = 17.6 | n = 4 ; % = 5 | n = 14 ; % = 20.3 |
| **BMI** | | | | |

| | Moderate COVID-19 (N = 47) | Severe-critical COVID-19 (N = 102) | Survived (N = 80) | Deceased (N = 69) |
|---|---|---|---|---|
| Custom value | NA | NA | NA | NA |
| **Use of immune suppressing treatments** | | | | |
| Custom value | NA | NA | NA | NA |
| **Socioeconomic status** | | | | |
| Custom value | NA | NA | NA | NA |
| **Previous history of COVID-19** | | | | |
| Custom value | NA | NA | NA | NA |
| **Other supplement use** | | | | |
| Custom value | NA | NA | NA | NA |
| **Timing of vitamin D measurements** | | | | |
| Custom value | NA | NA | NA | NA |
| **Shielding status** | | | | |
| Custom value | NA | NA | NA | NA |
| **Living in care homes** | | | | |
| Custom value | NA | NA | NA | NA |
| **Smokers** | | | | |
| Sample Size | n = 10 ; % = 21.3 | n = 41 ; % = 40.2 | n = 21 ; % = 26.3 | n = 30 ; % = 43.5 |

**Outcomes**

**Vitamin D level and status**

| | Moderate COVID-19 | Severe-critical COVID-19 | Survived | Deceased |
|---|---|---|---|---|
| | N = 47 | N = 102 | N = 80 | N = 69 |
| 25(OH)D level *(ng/mL)*<br>*Polarity: Not set* | | | | |
| Mean/SD | 26.3 (8.4) | 10.1 (6.2) | 19.3 (11.2) | 10.4 (6.4) |
| Vitamin D status<br>*Polarity: Not set* | | | | |

| | Moderate COVID-19 | Severe-critical COVID-19 | Survived | Deceased |
|---|---|---|---|---|
| | N = 47 | N = 102 | N = 80 | N = 69 |
| ≤20 | | | | |
| Sample Size | n = 8 ; % = 17 | n = 95 ; % = 93.1 | n = 39 ; % = 48.8 | n = 64 ; % = 92.8 |
| 21-29 | | | | |
| Sample Size | n = 27 ; % = 57.4 | n = 7 ; % = 6.9 | n = 29 ; % = 6.3 | n = 5 ; % = 7.2 |
| ≤30 | | | | |
| Sample Size | n = 12 ; % = 25.5 | n = 0 ; % = 0 | n = 12 ; % = 15 | n = 0 ; % = 0 |

**Univariate and multivariable logistic regression analysis showing independent predictors of in-hospital mortality**

Univariate analyses were conducted on age and comorbidities to assess if they were independently correlated with mortality from COVID-19. Serum 25(OH)D concentration was included in a multivariable model controlling for age and comorbidities.

| | Deceased vs Survived |
|---|---|
| | N1 = 69, N2 = 80 |
| Age<br>*Polarity: Lower values are better* | |
| Odds ratio/95% CI | 1.04 (1.01 to 1.06) |
| Smoking<br>*Polarity: Lower values are better* | |
| Odds ratio/95% CI | 2.16 (1.09 to 4.3) |
| Hyperlipidaemia<br>*Polarity: Lower values are better* | |
| Odds ratio/95% CI | 3.12 (1.45 to 6.72) |
| Diabetes<br>*Polarity: Lower values are better* | |
| Odds ratio/95% CI | 2.4 (1.23 to 4.68) |
| Chronic kidney disease<br>*Polarity: Lower values are better* | |
| Odds ratio/95% CI | 3.22 (1.35 to 7.66) |
| Chronic atrial fibrillation<br>*Polarity: Lower values are better* | |

| | Deceased vs Survived |
|---|---|
| | N1 = 69, N2 = 80 |
| Odds ratio/95% CI | 9.05 (1.97 to 41.72) |
| Congestive heart failure<br>*Polarity: Lower values are better* | |
| Odds ratio/95% CI | 4.84 (1.51 to 15.49) |
| Acute kidney injury<br>*Polarity: Lower values are better* | |
| Odds ratio/95% CI | 4 (1.23 to 13.05) |
| eGFR<br>*Polarity: Lower values are better* | |
| Odds ratio/95% CI | 0.98 (0.97 to 0.99) |
| 25(OH)D level<br>Univariate<br>*Polarity: Lower values are better* | |
| Univariate | |
| Odds ratio/95% CI | 0.9 (0.86 to 0.94) |
| Multivariable | |
| Odds ratio/95% CI | 0.93 (0.88 to 0.98) |

| Section | Question | Answer |
|---|---|---|
| Study participation | Summary Study participation | Moderate risk of bias<br>*(No descriptive statistics on ethnicity or BMI.)* |
| Study Attrition | Study Attrition Summary | Low risk of bias |
| Prognostic factor measurement | Prognostic factor Measurement Summary | Low risk of bias |
| Outcome Measurement | Outcome Measurement Summary | Low risk of bias |
| Study Confounding | Study Confounding Summary | Moderate risk of bias<br>*(Ethnicity and BMI not reported.)* |

| Section | Question | Answer |
|---|---|---|
| Statistical Analysis and Reporting | Statistical Analysis and Presentation Summary | Low risk of bias |
| Overall risk of bias and directness | Risk of Bias | Moderate<br>*(Important confounders of ethnicity and BMI was not reported as baseline characteristics nor used in the multivariable model assessing the association between 25(OH)D level and mortality.)* |
| | Directness | Partially applicable<br>*(Historic vitamin D measurements used)* |