Supplementary Table 1 Weighted Kappa values between eVai and Franklin for each of the 20 severe COVID-19 samples. Each entry includes the Kappa statistic, corresponding P-value, lower and upper confidence intervals (CI), indicating the degree of agreement between the two variant interpretation tools.

Sample	Kappa statistic	P-value	Lower CI	Upper CI
CVD1	0.2618	2.245e-117	0.2395	0.2841
CVD2	0.2963	1.284e-94	0.2682	0.3245
CVD3	0.2025	2.397e-92	0.1831	0.2220
CVD4	0.2284	8.951e-114	0.2087	0.2482
CVD12	0.2075	9.596e-101	0.1884	0.2266
CVD20	0.2510	6.523e-108	0.2287	0.2733
CVD21	0.3250	3.262e-123	0.2981	0.3520
CVD22	0.2529	1.025e-102	0.2299	0.2759
CVD23	0.3622	8.425e-119	0.3316	0.3929
CVD26	0.2724	3.304e-132	0.2505	0.2942
CVD27	0.2784	8.350e-140	0.2567	0.3001
CVD29	0.3225	1.871e-139	0.2974	0.3476
CVD30	0.3187	2.106e-143	0.2942	0.3432
CVD38	0.4070	3.528e-98	0.3691	0.4449
CVD39	0.3124	7.499e-115	0.2856	0.3393
CVD40	0.2934	1.312e-111	0.2678	0.3191
CVD42	0.3108	6.544e-97	0.2816	0.3399
CVD43	0.3082	1.584e-111	0.2813	0.3351
CVD45	0.3178	2.293e-138	0.2930	0.3427
CVD46	0.2713	1.332e-130	0.2494	0.2931
All variants	0.2281	0	0.2208	0.2353

CVD3 Genes Comparison

2.2%
(60)

1.9%
(52)

95.9%
(2619)

eVai

Franklin

CVD3 Variants Comparison

Franklin

eVai

9.63%
(481)

81.6%
(4076)

8.73%
(436)

CVD3 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

52.9%
(9)

23.5%
(4)

23.5%
(4)

CVD3 VUS Variants Comparison

50.2%
(1633)

46%
(1494)

3.78%
(123)

eVai

Franklin

CVD3 Benign/ Likely Benign Variants Comparison

Franklin

eVai

63.3%
(1626)

31.9%
(820)

4.71%
(121)

CVD4 Genes Comparison

2.67%
(81)

2.21%
(67)

95.1%
(2886)

eVai

Franklin

CVD4 Variants Comparison

Franklin

eVai

9.33%
(499)

82.4%
(4411)

8.24%
(441)

CVD4 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

61.5%
(8)

23.1%
(3)

15.4%
(2)

CVD4 VUS Variants Comparison

47.8%
(1700)

48.2%
(1715)

3.97%
(141)

eVai

Franklin

CVD4 Benign/ Likely Benign Variants Comparison

Franklin

eVai

63.1%
(1694)

31.7%
(850)

5.25%
(141)

CVD12 Genes Comparison

2.25%
(62)

1.89%
(52)

95.9%
(2639)

eVai

Franklin

CVD12 Variants Comparison

Franklin

eVai

9.07%
(443)

82.7%
(4041)

8.21%
(401)

CVD12 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

80%
(12)

6.67%
(1)

13.3%
(2)

CVD12 VUS Variants Comparison

3.42%
(110)

51.5%
(1654)

45.1%
(1448)

eVai

Franklin

CVD12 Benign/ Likely Benign Variants Comparison

Franklin

eVai

4.3%
(111)

63.7%
(1645)

32%
(825)

CVD20 Genes Comparison

2.17%
(54)

1.89%
(47)

95.9%
(2383)

eVai

Franklin

CVD20 Variants Comparison

Franklin

eVai

9.93%
(463)

81%
(3775)

9.09%
(424)

CVD20 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

18.2%
(2)

81.8%
(9)

CVD20 VUS Variants Comparison

4.28%
(129)

46.7%
(1408)

49%
(1478)

eVai

Franklin

CVD20 Benign/ Likely Benign Variants Comparison

Franklin

eVai

61.2%
(1399)

33.2%
(758)

5.64%
(129)

CVD21 Genes Comparison

2.09%
(50)

1.88%
(45)

96%
(2293)

eVai

Franklin

CVD21 Variants Comparison

Franklin

eVai

9.06%
(376)

83.1%
(3448)

7.88%
(327)

CVD21 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

66.7%
(16)

16.7%
(4)

16.7%
(4)

CVD21 VUS Variants Comparison

4.54%
(129)

36.4%
(1034)

59.1%
(1678)

eVai

Franklin

CVD21 Benign/ Likely Benign Variants Comparison

Franklin

eVai

58.3%
(1019)

34.5%
(602)

7.21%
(126)

CVD22 Genes Comparison

2.47%
(64)

2.16%
(56)

95.4%
(2474)

eVai

Franklin

CVD22 Variants Comparison

Franklin

eVai

9.6%
(450)

81.7%
(3829)

8.74%
(410)

CVD22 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVa

76.5%
(13)

11.8%
(2)

11.8%
(2)

CVD22 VUS Variants Comparison

4.08%
(128)

44.6%
(1399)

51.3%
(1609)

eVai

Franklin

CVD22 Benign/ Likely Benign Variants Comparison

Franklin

eVai

62.9%
(1388)

31.2%
(689)

5.8%
(128)

CVD23 Genes Comparison

2.45%
(50)

2.01%
(41)

95.5%
(1950)

eVai

Franklin

CVD23 Variants Comparison

Franklin

eVai

10.1%
(365)

80.9%
(2920)

9.03%
(326)

CVD23 Benign/ Likely Benign Variants Comparison

Franklin

eVai

56.2%
(786)

35.2%
(493)

8.58%
(120)

CVD23 VUS Variants Comparison

33.2%
(804)

61.8%
(1498)

5.03%
(122)

eVai

Franklin

CVD23 Benign/ Likely Benign Variants Comparison

Franklin

eVai

56.2%
(786)

35.2%
(493)

8.58%
(120)

CVD26 Genes Comparison

2.88%
(85)

2.51%
(74)

94.6%
(2792)

eVai

Franklin

CVD26 Variants Comparison

Franklin

eVai

7.82%
(382)

85.3%
(4169)

6.89%
(337)

CVD26 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

53.1%
(17)

37.5%
(12)

9.38%
(3)

CVD26 VUS Variants Comparison

3.58%
(123)

41.3%
(1419)

55.1%
(1896)

eVai

Franklin

CVD26 Benign/ Likely Benign Variants Comparison

Franklin

eVai

62.6%
(1404)

32%
(717)

5.44%
(122)

CVD27 Genes Comparison

2.54%
(79)

95.4%
(2964)

eVai

Franklin

2.03%
(63)

CVD27 Variants Comparison

Franklin

eVai

7.92%
(423)

85.1%
(4547)

6.98%
(373)

CVD27 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

66%
(31)

12.8%
(6)

21.3%
(10)

CVD27 VUS Variants Comparison

4.01%
(153)

39.3%
(1499)

56.7%
(2159)

eVai

Franklin

CVD27 Benign/ Likely Benign Variants Comparison

Franklin

eVai

62.7%
(1468)

31.2%
(730)

6.11%
(143)

CVD29 Genes Comparison

2.61%
(81)

95.2%
(2949)

eVai

Franklin

2.23%
(69)

CVD29 Variants Comparison

Franklin

eVai

8.66%
(445)

83.6%
(4292)

7.77%
(399)

CVD29 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVa

75%
(27)

8.33%
(3)

16.7%
(6)

CVD29 VUS Variants Comparison

4.61%
(168)

31.5%
(1150)

63.9%
(2328)

eVai

Franklin

CVD29 Benign/ Likely Benign Variants Comparison

Franklin

eVai

58.2%
(1123)

33.4%
(643)

8.4%
(162)

CVD30 Genes Comparison

2.39%
(81)

2.07%
(70)

95.5%
(3238)

eVai

Franklin

CVD30 Variants Comparison

Franklin

eVai

7.5%
(430)

85.8%
(4923)

6.66%
(382)

CVD30 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

61.8%
(21)

26.5%
(9)

11.8%
(4)

CVD30 VUS Variants Comparison

4.68%
(199)

30.6%
(1299)

64.7%
(2751)

eVai

Franklin

CVD30 Benign/ Likely Benign Variants Comparison

Franklin

eVai

59.8%
(1279)

31%
(664)

9.16%
(196)

CVD38 Genes Comparison

2.95%
(37)

2.63%
(33)

94.4%
(1186)

eVai

Franklin

CVD38 Variants Comparison

Franklin

eVai

12.3%
(326)

76.9%
(2033)

10.7%
(284)

CVD38 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVa

68.8%
(11)

31.2%
(5)

CVD38 VUS Variants Comparison

31.6%
(532)

63.5%
(1070)

4.93%
(83)

eVai

Franklin

CVD38 Benign/ Likely Benign Variants Comparison

Franklin

eVai

55%
(521)

36.7%
(348)

8.24%
(78)

CVD39 Genes Comparison

2.45%
(55)

2.22%
(50)

95.3%
(2143)

eVai

Franklin

CVD39 Variants Comparison

Franklin

eVai

8.76%
(350)

83.5%
(3337)

7.71%
(308)

CVD39 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

53.3%
(8)

33.3%
(5)

13.3%
(2)

CVD39 VUS Variants Comparison

4.19%
(115)

39.1%
(1073)

56.7%
(1558)

eVai

Franklin

CVD39 Benign/ Likely Benign Variants Comparison

Franklin

eVai

60.4%
(1065)

33.2%
(586)

6.41%
(113)

CVD40 Genes Comparison

2.69%
(65)

2.28%
(55)

95%
(2296)

eVai

Franklin

CVD40 Variants Comparison

Franklin

eVai

8.8%
(386)

83.2%
(3649)

8.02%
(352)

CVD40 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

53.8%
(7)

23.1%
(3)

23.1%
(3)

CVD40 VUS Variants Comparison

38.5%
(1156)

56.6%
(1702)

4.92%
(148)

eVai

Franklin

CVD40 Benign/ Likely Benign Variants Comparison

Franklin

eVai

59.4%
(1149)

33.1%
(640)

7.5%
(145)

CVD42 Genes Comparison

2.82%
(50)

2.54%
(45)

94.6%
(1679)

eVai

Franklin

CVD42 Variants Comparison

Franklin

eVai

9.71%
(332)

81.7%
(2795)

8.57%
(293)

CVD42 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

56.5%
(13)

17.4%
(4)

26.1%
(6)

CVD42 VUS Variants Comparison

3.96%
(90)

39.4%
(895)

56.7%
(1288)

eVai

Franklin

CVD42 Benign/ Likely Benign Variants Comparison

Franklin

eVai

59.4%
(882)

34.9%
(518)

5.72%
(85)

CVD43 Genes Comparison

2.32%
(52)

2.14%
(48)

95.5%
(2140)

eVai

Franklin

CVD43 Variants Comparison

Franklin

eVai

9.64%
(401)

81.9%
(3405)

8.51%
(354)

CVD43 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

58.3%
(14)

20.8%
(5)

20.8%
(5)

CVD43 VUS Variants Comparison

38.4%
(1085)

56.7%
(1602)

4.82%
(136)

eVai

Franklin

CVD43 Benign/ Likely Benign Variants Comparison

Franklin

eVai

60.2%
(1071)

32.4%
(577)

7.36%
(131)

CVD45 Genes Comparison

2.32%
(67)

1.91%
(55)

95.8%
(2765)

eVai

Franklin

CVD45 Variants Comparison

Franklin

eVai

8.55%
(445)

84%
(4368)

7.48%
(389)

CVD45 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

60%
(15)

12%
(3)

28%
(7)

CVD45 VUS Variants Comparison

35.3%
(1298)

59.5%
(2187)

5.17%
(190)

eVai

Franklin

CVD45 Benign/ Likely Benign Variants Comparison

Franklin

eVai

59.5%
(1284)

31.9%
(689)

8.53%
(184)

CVD46 Genes Comparison

2.55%
(82)

2.08%
(67)

95.4%
(3065)

eVai

Franklin

CVD46 Variants Comparison

Franklin

eVai

8.03%
(446)

84.8%
(4710)

7.18%
(399)

CVD46 Pathogenic/ Likely Pathogenic Variants Comparison

Franklin

eVai

47.4%
(9)

10.5%
(2)

42.1%
(8)

CVD46 VUS Variants Comparison

4.68%
(185)

38.2%
(1509)

57.1%
(2255)

eVai

Franklin

CVD46 Benign/ Likely Benign Variants Comparison

Franklin

eVai

61.6%
(1501)

31.1%
(758)

7.3%
(178)