
Ai Kido, Hiroshi Tamura, Hanako Ohashi Ikeda, Masahiro Miyake, Shusuke Hiragi, Akita Tsujikawa

ABSTRACT

Aims The latest evidence in the incidence of central retinal artery occlusion (CRAO) is needed to support the development of novel treatments as orphan drugs. However, up-to-date information on the incidence of CRAO in the ageing or aged population is limited. We aimed to investigate the nationwide epidemiological and clinical characteristics of CRAO in Japan, using nationwide health insurance claims data.

Methods We analysed a total of 16 069 762 claims data in the sampling dataset of the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), which is the nationwide health insurance claims database of 127 million whole Japanese individuals. CRAO was identified using the International Classification of Diseases 10th edition diagnostic code H34.1. The crude incidence rates and age-standardised incidence rates of CRAO, according to the standard age-structure population of the WHO, were calculated.

Results The crude incidence rate of CRAO in Japan was 5.84 (95% CI, 5.71 to 5.97) per 100 000 person-years. With respect to the sex-related incidence, the rate was higher 1.40 times in men than in women (6.85 (95% CI, 6.65 to 7.06) vs 4.88 (95% CI, 4.71 to 5.05), p<0.001). The age-standardised incidence rate was 2.53 (95% CI, 2.29 to 2.76) per 100 000 person-years.

Conclusions The crude incidence rate of CRAO was higher in Japan than in other countries, as reported previously, reflecting the Japanese population structure as a super-aged society. These findings can be helpful for the development of appropriate healthcare policies to address the increasing incidence of CRAO with the ageing population.

INTRODUCTION

Central retinal artery occlusion (CRAO) is a retinal vascular occlusive disease that results in ophthalmic emergencies likely to cause sudden-onset vision loss. Despite its significant potential health impact, there are no established treatments to improve visual acuity for CRAO, other than a few promising early treatment options. Accordingly, novel treatment modalities are needed; in this context, up-to-date data on the incidence of CRAO are needed to provide a theoretical basis for the development of such modalities. However, there are only few studies on CRAO and these are limited to before 2011 and reported low incidence rates. The most recent and largest study reported data from before 2011 and covered less than 50 million people, who were not included in the ageing society.

The National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) developed by the Japanese Ministry of Health, Labor and Welfare (MHLW) contains entire healthcare insurance claims data of almost all (≥95%) medical treatments in Japan. After 2011, more than 1.7 billion records from 127 million individuals are registered annually into the NDB.
MHLW started providing access to this data after a full anonymisation process for research purposes and decision making on health policies. Given the universal coverage health insurance system of Japan, the NDB represents a powerful tool to explore nationwide trends regarding CRAO.

The current study aimed to investigate the latest nationwide incidence of CRAO in Japan, a super-aged society, using the NDB sampling dataset during 2011 and 2015.

**METHODS**

**Study design**
The need for informed consent was waived owing to the use of legally anonymised data. This nationwide survey obtained permission from the MHLW to use the health insurance claims data in the NDB.

This study investigated the incidence of CRAO according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The REporting of studies Conducted using Observational Routinely collected health Data statement guidelines, the NDB sampling dataset covers 1/30 of all outpatient claims data and 1/30 of all inpatient claims data.

**NDB sampling dataset**
The National Database (NDB) contains detailed information of almost all medical claims data in Japan, including the diagnosis and medical treatments such as prescription, injection, examination and surgery for both outpatients and inpatients. As a sampling dataset, randomly selected claims data covering 1% of all outpatients and 10% of all inpatients in January, April, July and October from 2011 to 2015 were obtained from the MHLW for research purposes (available at https://www.mhlw.go.jp/file/06-Seisakujouhou-12400000-Hokenkyoku/0000164248.pdf, in Japanese, accessed 28 February 2020). In the current study, a total of 16 069 762 claims data as an NDB sampling dataset from the entire NDB dataset were analysed. The details of the NDB sampling dataset, including the data handling, is described in the online supplemental methods.

**Definition of primary inpatient and secondary inpatient**
A substantial percentage of patients with CRAO were reported to have other major active diseases, including acute myocardial infarction, symptomatic carotid stenosis and giant cell arteritis, and to develop CRAO even during hospitalisation. In the following incidence count process for CRAO, since it is necessary to separately calculate inpatient data of those who were hospitalised primarily for CRAO purposes and of those who developed CRAO while hospitalised for other diseases, we defined them as *primary inpatient* and *secondary inpatient*, respectively, as detailed in the online supplemental methods.

**Incidence of CRAO in the NDB sampling dataset**
CRAO was determined according to the International Classification of Diseases, 10th edition diagnostic code of H34.1. The onset was determined according to the month when the claim data were filed, and the month of CRAO onset was accordingly considered as the index month. Because almost all patients in the Japanese medical system visit outpatient departments before hospital admission, outpatient data alone should be enough to identify the incidence of CRAO. However, some of the inpatient data must be added in rare exceptional cases detailed in the online supplemental methods: 20% addition for emergently admitted inpatients on the day of first consultation without referral (primary inpatients) and 100% addition for patients hospitalised for other diseases at the onset of CRAO (secondary inpatients). The estimated total CRAO patients is calculated by multiplying the number of *outpatients* by 300 plus 20% of the *primary inpatients* and 100% of the *secondary inpatients* by 30, because the NDB sampling dataset covers 1/300 of all outpatient claims data and 1/30 of all inpatient claims data.

**Population at risk**
The Current Population Estimates as of 1 October 2013 by the Japanese Ministry of Internal Affairs and Communications were used to define the entire population and each sub-group population as the population at risk (available at https://www.stat.go.jp/english/data/jinsui/2.html, accessed 28 February 2020).

**Incidence rate of CRAO**
The incidence rates for age stratified by 5-year categories and sex during the study period were determined by dividing the number of people who developed CRAO with the total population at risk within each group. The age-standardised incidence rate of CRAO was calculated according to the standard age-structure world population of the WHO for 2000–2025. The incidence rates of CRAO in age subgroups, that is, ≥50, 60 and 70 years were also calculated.

**Statistical analyses**
All statistical analyses were performed using R V.3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). All values are presented with 95% CIs based on the Poisson distribution.

**Patient and public involvement**
Patients were not involved in the design, analyses and interpretation of this study.

**RESULTS**
A total of 119 outpatients, 132 primary inpatients and 23 secondary inpatients with CRAO were identified throughout the 5-year study period. Table 1 shows the number of CRAO cases identified in the current dataset and the estimated incidence of CRAO stratified by age. The incidence of CRAO was higher 1.40 times in men than in women (6.85 (95% CI, 6.65 to 7.06) vs 4.88 (95% CI, 4.71 to 5.05) per 100 000 person-years, p<0.001). The incidence of CRAO was also higher in men than in women in most age groups (figure 1).
Table 1  Frequencies, estimated numbers and incidence rates of clinically diagnosed CRAO in Japan from 2011 to 2015, as determined from the National Database of the Health Insurance Claims and Specific Health Checkups of Japan

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Japanese population*</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>Outpatient</th>
<th>Primary inpatients†</th>
<th>Secondary inpatients‡</th>
<th>Estimated total§</th>
<th>Incidence rate 95% CI</th>
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<td>2684</td>
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<td>2743</td>
<td>2618</td>
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<td>0</td>
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<td>0</td>
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<td>10–14</td>
<td>5790</td>
<td>2967</td>
<td>2823</td>
<td>1</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.21</td>
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<tr>
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<td>6047</td>
<td>3098</td>
<td>2949</td>
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<td>3181</td>
<td>3123</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>0</td>
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<td>25–29</td>
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<td>3506</td>
<td>3365</td>
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<td>1</td>
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<td>35–39</td>
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<td>4467</td>
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<td>4</td>
<td>0</td>
<td>3</td>
<td>6</td>
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<td>40–44</td>
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<td>4888</td>
<td>4979</td>
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<td>3</td>
<td>1</td>
<td>6</td>
<td>8</td>
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<td>45–49</td>
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<td>4177</td>
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<td>3840</td>
<td>3892</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>9</td>
<td>7</td>
<td>19.44</td>
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<td>60–64</td>
<td>9865</td>
<td>4740</td>
<td>4925</td>
<td>14</td>
<td>8</td>
<td>1</td>
<td>4728</td>
<td>8</td>
<td>20.64</td>
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<td>65–69</td>
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<td>4183</td>
<td>4517</td>
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<td>18</td>
<td>2</td>
<td>5268</td>
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<td>70–74</td>
<td>7997</td>
<td>3537</td>
<td>4060</td>
<td>25</td>
<td>29</td>
<td>6</td>
<td>2654</td>
<td>20</td>
<td>17.06</td>
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<td>75–79</td>
<td>6301</td>
<td>2772</td>
<td>3529</td>
<td>22</td>
<td>20</td>
<td>4</td>
<td>8840</td>
<td>21</td>
<td>16.72</td>
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<tr>
<td>80–84</td>
<td>4763</td>
<td>1889</td>
<td>2874</td>
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<td>14.89</td>
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<tr>
<td>85–89</td>
<td>2925</td>
<td>970</td>
<td>1955</td>
<td>9</td>
<td>10</td>
<td>1</td>
<td>2790</td>
<td>19</td>
<td>17.49</td>
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<tr>
<td>90–94</td>
<td>1216</td>
<td>283</td>
<td>933</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>836</td>
<td>15</td>
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<tr>
<td>95–99</td>
<td>350</td>
<td>61</td>
<td>289</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
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<td>&gt;100</td>
<td>55</td>
<td>7</td>
<td>48</td>
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<td>0</td>
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<td>0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Continued
Among the patients with clinically diagnosed CRAO, 13% (estimated inpatients: 4650=(132+23)×30/estimated total:37 182) were hospitalised and supposedly treated or examined intensively.

Table 2 shows the incidence rates of CRAO per 100 000 person-years. The crude incidence of CRAO in Japan was 5.84 (95% CI, 5.71 to 5.97) for the overall population, 6.85 (95% CI, 6.65 to 7.06) for men and 4.88 (95% CI, 4.71 to 5.05) for women. The age-standardised incidence rate was 2.53 (95% CI, 2.29 to 2.76). Meanwhile, the incidence rates were 11.93, 15.29 and 19.17 in those aged ≥50, 60 and 70 years, respectively. The male-to-female ratios in those aged ≥50 years, ≥60 years and ≥70 years were 1.56, 1.85 and 1.96, respectively. The incidence rate of CRAO increased as the age increased.

DISCUSSION

Japan, which has a population of over 120 million, is a super-aged society by the WHO definition, with people aged ≥65 years accounting for over 21% of the total population. Accordingly, healthcare policies on ageing-related diseases are important. However, recent data on the incidence of CRAO, which can be helpful in developing health-related policies, are lacking in Japan. To our best knowledge, the current study is the first nationwide, population-based epidemiological study of CRAO in an ageing or aged society. We found that the crude incidence rates and age-standardised incidence rates of CRAO were 5.84 and 2.53 per 100 000 person-years, respectively. These results provide recent instrumental evidence on the incidence of clinically diagnosed CRAO in Japan and can thus be used as theoretical basis for developing appropriate treatment modalities.

The crude incidence rate of CRAO was 5.84 (95% CI, 5.71 to 5.97) per 100 000 person-years, which was relatively higher than rates in previous reports.3 10 11 The differences may be due to the chronological differences of the research periods. However, compared with the age-standardised incidence rates of the WHO (2000–2025) standard population, the current study found a 2.53 (95% CI, 2.29 to 2.76) incidence rate. The age-standardised incidence rate is comparable to that of South Korea (2.06) and Olmsted County (1.87)3 11 and to projections in the Korean population in 2020 (2.37) and 2030 (3.63) per 100 000 person-years.11 We also found that the incidence rate of CRAO increased with increased age, consistent with previous studies.3 11 The incidence rate of CRAO also increased in those aged 50, 60 and ≥70 years. Collectively, our results and those of previous studies indicate that CRAO is more common in the elderly. Further, the high crude incidence of CRAO in the Japanese, who are rapidly ageing, suggests that the incidence of CRAO will increase in all ageing countries.

In the total estimated CRAO incidence calculation, 20% of primary inpatient CRAO patients were added to outpatient CRAO incidence, referring to the results of
the Patient’s Behavior Survey conducted by MHLW as described in the online supplemental methods. Because the 20% figure, however, was not sufficiently validated, we also calculated 0% and 100% primary inpatient CRAO addition to the outpatient CRAO as the possible range. The crude incidence rate of CRAO from 5.72 to 6.34, while the age-adjusted incidence rate of CRAO ranged from 2.47 to 2.74. These possible ranges were mostly within the 95% CI of the most likelihood model with a 20% figure. Indeed the 20% figure was obtained from a survey for all diseases, not for a CRAO-specific survey. If more specific and accurate reports are available in the future, the incidence rate of CRAO will need to be recalculated.

In the current study, only 13% of the patients with clinically diagnosed CRAO were hospitalised and supposedly

Table 2  Incidence rates of CRAO per 100 000 person-years in the current and previous studies

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence rate</td>
<td>95% CI</td>
<td>Incidence rate</td>
</tr>
<tr>
<td>Crude</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan (current study)</td>
<td>5.84</td>
<td>5.71 to 5.97</td>
<td>6.85</td>
</tr>
<tr>
<td>Aged ≥50 years</td>
<td>11.93</td>
<td>11.64 to 12.21</td>
<td>14.81</td>
</tr>
<tr>
<td>Aged ≥60 years</td>
<td>15.29</td>
<td>14.92 to 15.67</td>
<td>20.57</td>
</tr>
<tr>
<td>Aged ≥70 years</td>
<td>19.17</td>
<td>18.61 to 19.73</td>
<td>26.95</td>
</tr>
<tr>
<td>Olmsted County in the USA*</td>
<td>1.33</td>
<td>0.60 to 1.71</td>
<td>2.15</td>
</tr>
<tr>
<td>South Korea*</td>
<td>1.80</td>
<td>1.74 to 1.86</td>
<td>2.15</td>
</tr>
<tr>
<td>Croatia*</td>
<td>0.7</td>
<td>0.2 to 1.7 (range)</td>
<td></td>
</tr>
<tr>
<td>Age-standardised</td>
<td>2.53</td>
<td>2.29 to 2.76</td>
<td>1.87</td>
</tr>
<tr>
<td>Olmsted County in USA*</td>
<td>2.06</td>
<td></td>
<td>2.06</td>
</tr>
<tr>
<td>South Korea in 2020 (projected)*</td>
<td>2.37</td>
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<td>2.37</td>
</tr>
<tr>
<td>South Korea in 2030 (projected)*</td>
<td>3.63</td>
<td></td>
<td>3.63</td>
</tr>
</tbody>
</table>

*The incidence rates of CRAO in other countries and areas were obtained from previous reports: Olmsted County, Minnesota, USA between 1976 and 2005; South Korea between 2008 and 2011 and Croatia between 1984 and 1999.
treated or examined intensively. Also in the past report, only 18% of retina specialists pursue a hospital-based evaluation, defined as hospital admission or emergency room evaluation, while 75% of neurologists did.25 American Heart Association and the American Stroke Association define retinal artery occlusion as an ischaemic stroke and amaurosis fugax as a retinal transient ischaemic attack, and recommend imaging and evaluating all these patient for treatable conditions such as carotid stenosis and atrial fibrillation in the guidelines.24 25 Despite the recommendations in the guidelines, ophthalmologists in both USA and Japan were not fully aware of the need for systemic examination after CRAO.

While the current study has the advantage owing to the exclusiveness of the dataset in the insured healthcare service of a country, some limitations must be acknowledged when interpreting the findings. First, the accuracy of the CRAO diagnosis based on the ICD-10 codes was not sufficient, which is inherent to studies using claims data. Ideally, we would have validated the CRAO diagnosis by the medical records and then performed the research with high diagnostic accuracy. Second, a small portion of cases, under 5% of all insured healthcare services of Japan, are not included in the NDB database,12 which may lead to an underestimation of the actual incidence of CRAO. Third, because a hashed personal identification number was provided only in the outpatient data, we could not exclude any potential preexisting cases of CRAO nor eliminate the overlap between outpatient and inpatient data, although we considered it in the calculation of incidence (online supplemental methods). This might lead to overestimation of the incidence of CRAO. Finally, characteristics of the NDB sampling dataset, including full anonymisation and strict control over access, prevented more detailed discussions. The available data were limited to 2011–2015, which was a barrier to comparison with the previous reports. In addition to more accurate estimation of CRAO incidence, risk factor evaluation for CRAO or accuracy assessments in CRAO diagnosis by stratified specialty could be performed beyond the achievement of consolidated personal identification number and relaxation of access restrictions.

In conclusion, the current study provides the nationwide incidence rate of CRAO in Japan, a super-aged society, based on 5-year population-based NDB sampling dataset. The crude incidence of CRAO in Japan was 5.84 (95% CI, 5.71 to 5.97) per 100 000 person-years and was higher than in other countries and areas as reported previously, reflecting the Japanese population structure as a super-aged society. These findings can be helpful for the development of appropriate healthcare policies to address the increasing incidence of CRAO with the ageing population.

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**Contributors**

HOI had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AK, HT and HOI conceptualised and designed the data. HOI involved in acquisition of data. AK, HT, HOI, MM, SH and AT involved in analysis, or interpretation of data. AK and HT involved in drafting of the manuscript. HOI, MM, SH and AT involved in critical review of the manuscript for important intellectual content. HOI and AT involved in administrative, technical or material support. AT involved in supervision.

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**Disclaimer**

The funding organisation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

**Competing interests**

HOI reports receiving grants from the Japan Agency for Medical Research and Development during the conduct of the study.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not required.

**Ethics approval**

This study was approved by the Institutional Review Board and by the Ethics Committee of Kyoto University Hospital and Kyoto University Graduate School of Medicine (No. R2405). All investigations were conducted according to the tenets of the Declaration of Helsinki and its later amendments.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

Data may be obtained from a third party and are not publicly available. After the authorised research period, the raw data of the NDB sampling data must be returned to the MHLW. Thus, researchers have access only to protocols and programme code but no longer to the raw data. Thus the data sharing would be limited to the programme code. Those who want to access raw data needs to apply to MHLW.

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