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Infrared Thermal Imaging of Patients With Acute Upper Respiratory Tract Infection: Mixed Methods Analysis

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Abstract

Background: Upper respiratory tract infection is a common disease of the respiratory system. Its incidence is very high, and it can even cause pandemics. Infrared thermal imaging (IRTI) can provide an objective and quantifiable reference for the visual diagnosis of people with acute respiratory tract infection, and it can function as an effective indicator of clinical diagnosis.

Objective: The aims of this study are to observe and analyze the infrared expression location and characteristics of patients with acute upper respiratory tract infection through IRTI technology and to clearly express the quantification of temperature, analyze the role of IRTI in acute upper respiratory tract diagnostic research, and understand the impact of IRTI in qualitative and quantitative research.

Methods: From December 2018 to February 2019, 154 patients with acute upper respiratory tract infection were randomly selected from the emergency department of the First Affiliated Hospital of Guangzhou Medical University. Among these patients, 73 were men and 81 were women. The subjects were divided into two groups according to the presence of fever, namely, fever and nonfever groups. Qualitative and quantitative analyses of the infrared thermal images were performed to compare the results before and after application of the technology.

Results: Using the method described in this paper, through the analysis of experimental data, we elucidated the role of IRTI in the diagnosis of acute upper respiratory tract infection, and we found that qualitative and quantitative IRTI analyses play important roles. Through the combination of theory and experimental data, the IRTI analysis showed good results in identifying acute upper respiratory tract infection.

Conclusions: IRTI technology plays an important role in identifying the infrared expression location and characteristics of patients with acute upper respiratory tract infection as well as in the quantification of clear expression of body temperature, and it provides an objective and quantifiable reference basis for elucidating the pathogenesis of these patients.

KEYWORDS

Introduction

Background

Acute upper respiratory infection is common in winter and spring. It can be spread through food droplets containing influenza virus or the use of virus-contaminated robotic arms and other tools [1,2]. These viruses may also cause local or large-scale global climate change and pandemics [3,4]. Because the antigen on the surface of this subtype of human virus can readily directly undergo immune mutation, new immune subtypes are generated, and there is no possibility of direct crossover between different novel subtypes for immunization. Therefore, the disease can not only occur repeatedly within one year in the same person but can also cause widespread epidemics in a few years [5,6].

Far-infrared thermal imaging is a noninvasive, nontoxic, and objective temperature measurement method that can provide information on changes in the function of the parasympathetic nervous system [7]. By collecting the far-infrared radiation heat from the human body, determining an intuitive temperature, processing a color map through a computer, and using different colors to represent different human body surface temperature distributions, the temperature distribution changes of the human body can be accurately measured according to the difference between normal and abnormal infrared radiation [8]. Based on the scope and location of the focus, this is a functional image that can reflect the metabolism of the body; however, the observation of subtle changes in tissue structure using this method is not as accurate as that using computed tomography or magnetic resonance imaging [9,10]. Temperature is an important indicator that can reflect the pathophysiological state of the human body. The skin temperature of the normal human body is basically symmetrical from the limbs to the head and face [11]. When people contract diseases, the metabolism of local tissues and cells changes first, prior to changes in human function or morphology. Moreover, before anatomical structure changes, molecular biology changes occur in lesions and their surrounding tissues, which will further change the normal temperature of the lesion. The spatial distribution and gradient change of temperature will further reflect the specific scope of the disease and reveal the nature of the occurrence and development of the disease [12]. Far-infrared thermal imaging technology is based on this principle; through a series of computer analyses and the use of image processing technology to collect infrared information, thermal images can be formed using different colors to display the temperature distribution of the human surface [13].

Infrared Thermal Imaging

Infrared thermal imaging (IRTI) temperature measurement technology was developed on the basis of the development of an infrared focal plane array. An IRTI temperature measurement system is a 2D thermal imaging temperature measurement device [14]. The system detects and displays the distribution of infrared radiation energy density based on between the target and the environment according to the gray value of the gray image. At present, there are two main types of infrared detectors: photon detectors and thermal detectors. Photon detectors include photoelectric detectors, photoconductive detectors, and quantum detectors. The working performance of a photon radiation detector is only very good when the ambient temperature is very low. Thermal radiation detectors mainly include thermocouples, thermoelectric reactors, thermal release relays and other detectors, as well as various thermal radiation heaters [15]. Thermal radiation detectors have relatively broad control requirements for the temperature of specific working environments. These detectors can usually function normally at room temperature. Infrared detectors that can function at room temperature are often called uncooled infrared detectors because they do not require refrigeration equipment [16]. Pyroelectric detectors and thermal radiation calorimeters are two widely used instruments in thermal infrared detectors. Thermal radiation detectors are more mature than heaters for the measurement of electrical radiation. Infrared camera technology is an important product of the mature application and development of infrared focus plane imaging technology [17]. As a new type of automatic gas temperature measurement and control technology, one of the main features of infrared temperature measurement is the noncontact automatic measurement of gas temperature. In addition, compared with traditional temperature measurement methods, it has two advantages of low automatic temperature measurement and high accuracy. Compared with traditional infrared contact thermal temperature measurement system technology, the infrared contact temperature measurement method obviously has unparalleled technical advantages. Because of these advantages, infrared external temperature measurement control technology has been widely used in industrial fields in China, such as steel, power, forest engineering, fire protection, petrochemicals, and aerospace [18]. From the perspective of the historical development of infrared optical temperature measurement technology, the rapid development of instruments is mainly concentrated in two main aspects. The first aspect is the continuous development of optical technology. In recent years, the development of infrared optical temperature measurement instrument technology has been extremely rapid. With the continuous development of the cold infrared temperature measuring focal plane, it has advanced rapidly. The second aspect is the continuous development of infrared optical temperature measuring instruments. They are also being rapidly developed along with the continuous development of infrared optical temperature-measuring instrument technology [19,20].

The principle of an infrared thermometer is based on the principle of infrared radiation. Like other technologies, its development has progressed from simple to complex. The earliest infrared temperature measurement equipment could only measure the temperature of a certain point in the field of view, and the accuracy of the temperature measurement was not sufficiently high [21]. With the development of technology, the ability to measure temperature gradually improved; however, temperature measurement devices could not reflect the appearance and shape of the object under study, nor could they be used to determine the surface temperature distribution of the object. The specific reason is that infrared temperature measurement equipment did not enable infrared imaging at the time.

Features

Quick Temperature Measurement

Infrared thermometers respond very quickly to temperature and can be used for real-time and fast-track measurements. Because of this advantage, infrared temperature measurement technology is widely used in the steel and electricity industries, forest fire prevention, and many other aspects.

Wide Temperature Measurement Range

Infrared temperature measurement technology has a wider application range than traditional temperature measurement methods. In theory, infrared temperature measurement has no upper limit. In practical applications, infrared thermometers can measure low temperatures of tens of degrees below zero and high temperatures of thousands of degrees. There is no time limit; work can be performed at any time of day or night. Due to the characteristics of infrared technology, the ability to work at night has become a highlight of infrared thermometers. They can be used measure the temperature of microscopic targets. Infrared thermometers are not limited by the distance and can measure the temperature in a short distance or a long distance.

There are many methods of infrared temperature measurement. According to these different methods, current infrared temperature measuring instruments can be divided into two categories: one is infrared temperature measuring equipment based on full-field analysis; the other is infrared temperature measuring system based on point-by-point analysis. The principle of full magnetic field analysis is that the temperature distribution of the entire object is an infrared focal plane array imaging infrared lens, and the temperature distribution of the entire object constitutes the infrared thermal image of the object, and the infrared temperature measurement equipment of the complete field distribution is also called the infrared heat imager [22]. The measurement principle of point-by-point analysis is to focus part of the infrared radiation on an object through an infrared detector, and then according to the object with known surface emissivity, the radiant power of the object is converted into temperature information, and the phase can be easily measured by comparison. This point-by-point analysis system is usually called an infrared thermometer.

IRTI technology did not develop rapidly until the 1950s, and the development of infrared temperature measurement technology has since achieved a fundamental breakthrough [23]. The main function of an infrared thermometer is to measure temperature, and there are three main types: infrared point thermometers, infrared scanners, and infrared thermal television. Objects in nature with temperatures above absolute zero will usually emit a large amount of infrared heat radiation around the temperature measurement image; therefore, the infrared environment in the temperature measurement system may also directly affect the image accuracy of the temperature measurement of the object. This environmental impact factor can be roughly divided into two major parts: the subjective background environmental factor and the objective environmental factor. The background change factor mainly refers to the change difference between the target to be measured by a temperature signal measurement processing system and the surrounding temperature of the measurement background [24,25]. When the difference value is larger, the temperature measurement is more accurate; the natural environmental impact factors are mainly due to the direct impact of environmental factors such as direct solar ultraviolet radiation, direct ground radiation, and wind speed on the accuracy of atmospheric temperature standard measurement results [26]. When the infrared detector detects the target object, it requires the target to be different from the surrounding environment in at least one place for it to be detected by the detector. The greater the difference between the target and the environment, the easier it is to detect; the smaller the difference, the less likely it is to be detected. A comparison is made of the target environment. If the target object is placed in a specific background, then it will be affected by the background. At the same time, as the distance increases, the relative field of view of the same object decreases, which reduces the quality of the output signal and affects the accuracy of the temperature measurement [27].

Using a 2D image to display the 3D distribution of human body temperature takes advantage of the different characteristics of multisensor images and the complementary advantages of multisource images to fuse multisensor images into one image, thereby obtaining a more accurate description of the observed image, scene, or target [28,29]. At present, the most common and widely used image fusion technology is infrared and visible light image fusion. The infrared sensor uses the thermal radiation characteristics of the object itself to "actively" acquire the target information on the image, which has the characteristics of not being affected by the weather or light environment. However, at the same time, due to the limitations of imaging equipment, the spatial resolution and image contrast of infrared images are low, the reflectivity of target details is poor, and the imaging effect does not conform to human visual habits [30]; in contrast, visible light sensors can detect reflections in the scene. Under visible light, the obtained image has higher spatial resolution, clear texture information, and rich image details [31,32]. However, it can be readily disturbed by external factors, and a large amount of scene information will be lost in the case of turbid atmosphere and insufficient light. The fusion of infrared images and visible images can give full play to the advantages of infrared and visible images. The characteristics of these two images are complementary. While maintaining the anti-interference characteristics of infrared images, increasing the spatial details of the image is conducive to improving the detection and reconnaissance capabilities of the system and enhancing the ability of the image system to express the scene [33].

Infrared Point Thermometry

An infrared point thermometer is a nonimaging infrared thermometer. It can only measure the temperature of a very small area (which can be seen as a point). According to different design principles, infrared point thermometers can be divided into three categories: total radiation thermometers, colorimetric thermometers, and brightness thermometers [34]. Infrared spot thermometers have been available since the early 20th century. The narrow temperature measurement range of these thermometers is not suitable for measuring the temperature of large areas. When it is necessary to measure a large object, it

is very inconvenient to obtain multiple measurements of various parts of the object and perform manual scanning. However, these spot thermometers have become a powerful tool in many fields due to their low price and practical features. An infrared scanning instrument, as the name suggests, is an instrument used to detect the linear temperature of an object. The realization principle is generally to detect the temperature of the object through the movement of the object or the cooperation of the atmosphere [35]. Due to the difficulty of realizing infrared scanning instruments and their low commercial value, the application of these instruments is not very common at present. Infrared thermal television is related to infrared point thermometry. It can perform 2D temperature detection on objects, but it does not need to measure multiple points of objects as infrared thermometers do [36]. Its convenience far exceeds that of infrared thermometers. Moreover, its temperature detection does not require a cooling mechanism and can achieve better performance. However, there is a large gap between its technical indicators and infrared cameras. At present, not only single-color thermometers but also two-color thermometers are in use in China. The single-color thermometer can only determine the temperature by the energy of one band, while the two-color thermometer can finally determine the temperature by comparing the radiant energy of two different infrared bands; therefore, this method has strong anti-interference and adaptability [37]. Any object that exists in nature will emit infrared radiation as long as its temperature is above absolute zero. The energy radiation per unit time of the measured object on its surface elements can be expressed as:

$$T = \varepsilon\sigma^4$$

Infrared temperature measurement technology is a noncontact temperature measurement technology; it has many advantages compared with contact temperature measurement approaches. However, to reach the infrared detector, the infrared radiation emitted by the target object must pass through the atmosphere, and the atmosphere will absorb infrared light accordingly. At the same time, because of the differences in emissivity of the object, the reflection of the detector, and other factors, the infrared radiation received by the detector is not completely emitted by the target object [38].

In fact, the infrared radiation received by the infrared detector mainly includes the target's own radiation, atmospheric radiation, and environmental reflection [39]. To enable infrared wireless temperature measurement and monitoring system equipment to accurately measure indoor temperature in real time, it is necessary to statistically analyze the data of the main factors that affect the accuracy of the infrared wireless temperature measurement system. Passive detection of the infrared emissivity of a temperature-measuring object is usually a direct influencing factor that directly affects the temperature measurement of infrared rays [40]. The infrared emissivity of an object is usually an important measurement index that is used to characterize the thermal intensity of the measured object on the infrared radiation of its surface. For two objects with the same infrared temperature, the infrared surface temperature emissivity values are different, and the infrared temperature radiation may change; therefore, the infrared temperature radiation received by the

infrared radiation detector may also change, which directly affects the intuitive accuracy of the temperature radiation measurement of the object. The influence of the emitted optical power is closely related to many factors, such as the size of the emitting object, the surface temperature, and the wavelength of the light radiated from the object. The power of the surface laser emission is also related to the detection of the coating roughness of the surface of the object shell, the impurities of the chemical compounds and contaminants, and the thickness of the oxide layer of the object [41]. In general, the rougher the laser surface of the same textured object, the higher the value of the laser emissivity of the surface where it is located. In contrast, the smoother the surface object, the lower the surface emissivity. Therefore, it is difficult to measure the emissivity of the object surface very accurately. The atmosphere also contains many polymer gases that can absorb a large amount of infrared light at the same time [42], especially white gas containing water vapor, carbon dioxide, ozone, etc, in the surface layer of the earth's atmosphere, they can also absorb a large amount of infrared light and radiation at the same time, and the concentration of carbon dioxide containing water vapor and hydrogen in the earth's atmosphere is relatively high. In this way, the infrared target detection object mainly refers to the infrared ray radiation gas emitted by the earth. The small molecules that absorb these radiation gases are exposed to the earth's atmosphere, which greatly reduces the infrared radiation activity intensity of the infrared radiation detector; this not only directly affects the infrared temperature measurement accuracy of the sensitive temperature measurement and processing system but also may directly affect the temperature sensitivity of the infrared temperature sensitive measurement and processing system [39]. However, the atmosphere will also attenuate other factors that affect the accuracy of temperature measurement, such as the infrared radiation reflected by the surface of the object, which is much smaller than the infrared radiation intensity of the object itself. If the attenuation of the atmosphere can be fully used, the temperature measurement error can be reduced. Another reason for the attenuation of infrared radiation is the scattering of various gas molecules and suspended particles in the air.

Image fusion technology has important application prospects and substantial application value in both military and civilian fields. Image fusion is a comprehensive process that includes image acquisition, image transmission and image signal processing. Image acquisition and transmission require the functions of the image sensor and its related hardware circuits [43]. Image signal processing relies on software algorithms running on hardware platforms. The entire image fusion system is a complex system combining software and hardware. According to their working modes, infrared detectors can be divided into two categories: cooled infrared focal plane detectors and uncooled infrared focal plane detectors. The advantages of cooled infrared focal plane detectors are their high sensitivity and long detection distance; however, their use conditions are harsh and expensive [44]. At present, only a few of these detectors are used in high-end military equipment; uncooled infrared focal plane detectors can work directly at room temperature, are small in size, consume low power, and demonstrate fast startup; moreover, the price is only a small

part of the cooling type. Infrared radiation is very common in nature; however, because the wavelength of infrared radiation is invisible to the human eye, people cannot observe it. Therefore, people began to attempt to design infrared equipment, such as IRTI, to replace the human eye, extend the visual range of the human eye from visible light to the infrared band, and directly obtain the shape characteristics and temperature distribution of objects that cannot be observed in the visible light range. When the internal temperature of the object is in an unbalanced state, a heat transfer process occurs [45]. In this process, discontinuous measurements of the objects will affect or hinder the normal transmission and distribution of heat and the temperature differences of different areas on the surface of the object will then be measured, resulting in different temperature distribution patterns, that is, "hot spot" and "cold spot" thermal images. Because the temperature distribution can indirectly reflect the physical characteristics of the measured object, according to the basic law of infrared radiation, IRTI detection technology is processed by charge-coupled devices in infrared equipment, such as infrared cameras [46]. The infrared radiation signal containing the target defect information is converted into a visible light thermal image, and the defect information of the measured object is extracted in combination with the corresponding data processing method. At present, in the field of IRTI detection, the topics studied by researchers mainly include three aspects. The first aspect is the use of different excitation methods; the second is expansion of the scope of application; and the third is the optimization of thermal image processing. In the early research of thermal image data processing methods, the data processing method based on pulsed eddy current thermal imaging detection technology is generally to select the best thermal image to extract defect features and then complete the defect identification [47].

Acute Upper Respiratory Tract Infection

Upper respiratory tract infection is a common and frequent disease of the respiratory system. Its incidence is very high, it can spread in a small area, and it can even cause pandemics [48]. It can cause myocarditis, acute nephritis, encephalitis, and even respiratory distress syndrome. In recent years, the harm caused by severe acute respiratory syndrome (SARS) and H1N1 influenza to humans is still vivid. China has a high rate of acute upper respiratory tract infections.

IgG has antiviral, antibacterial, and complement fixation functions, and it participates in mucosal immunity through placenta and IgA [49]. The decline of IgG reduces the body's antibacterial and antiviral ability, which can easily lead to repeated respiratory infections. Increasing numbers of patients with repeated respiratory tract infections have low specific pneumococcal antibody levels or are unable to respond adequately to pneumococcal vaccines or natural infections. This may explain why many patients do not experience a decline in total immunoglobulin or immunoglobulin subclasses although immunodeficiency of pneumococcal and other capsular bacteria occurs. Any decrease in cellular immune function can cause respiratory infections. IL-2 can promote the transformation of T cells from the thymus and spleen to cytotoxic cells, thereby enhancing granulocyte antibody–dependent cell-mediated cytotoxicity [50]. At the same time, IL-2 has been found to have

antiviral effects and protect adults from Epstein-Barr virus infection. Therefore, in the treatment of respiratory tract infections, in addition to active antibiotic treatment, recombinant cytokines or cytokine antagonists should also be provided with an appropriate microenvironment to regulate the level of cytokines, change the immune response in the body, and achieve the purpose of treatment.

Smokers are twice as likely to have acute upper respiratory tract infections as nonsmokers [51]. Serum bilirubin levels may be an influencing factor. People with low levels of serum bilirubin are more likely to develop symptoms of acute upper respiratory tract infection.

Exposure of children to smoke can increase their incidence of lower respiratory tract infections (such as bronchitis and pneumonia) and can induce new asthma. A normal chemical composition in the atmosphere is a necessary condition to ensure human health. With the development of industrial production and transportation, the use of coal, oil and other energy sources has increased, and a large number of harmful substances are being scattered in the air [52]. Air pollution has become one of the main factors endangering human health [53]. Acquired risk factors include vitamins, trace element deficiency, diabetes, and other related factors. It was found that the content of vitamins A, E, and B and of carotene in the serum of children with repeated respiratory infections was significantly reduced. Vitamin A plays an important role in enhancing human immune function. In the absence of vitamin A, T cells may undergo nonspecific changes, and T cell proliferation may also be impaired. T cells play an irreplaceable role in various immune inflammatory responses. Calcium, magnesium, and other elements play an important role in regulating enzyme function, cell activity and body immunity. When the body lacks calcium, chronic respiratory diseases easily occur and are readily aggravated. Magnesium is involved in regulating immune function and increasing the body's resistance [54]. Diabetic patients are also susceptible to infection, and the infection is serious and difficult to control in these patients.

Aim of This Study

In this paper, we use experimental research methods to understand the impact of IRTI through qualitative and quantitative studies and a comparative exploration before and after the application of this technology; through theoretical analysis and experimental exploration, the role of IRTI in the diagnosis of acute upper respiratory tract infection can be elucidated. Data were recorded, sorted, calculated, plotted, and analyzed for processing, statistical analysis was performed on the IRTI data set, and empirical analysis of infrared expression using IRTI technology was performed for patients with acute upper respiratory tract infection. The location and characteristics, combined with the effective data, summarize and analyze the important role of IRTI technology in clearly expressing the quantification of temperature. The results show that with the method described in this paper, superior research results are obtained.

Methods

Experimental Data

From December 2018 to February 2019, 154 patients with acute upper respiratory infection were randomly selected in the emergency department of the First Affiliated Hospital of Guangzhou Medical University. The patients included 73 men and 81 women. According to fever, the subjects were divided into two groups: fever type and nonfever type. If the patient's axillary temperature reached the fever threshold (≥37.1 ℃), they were classified as fever type. Among the 154 participants, 76 were in the fever group; the ratio of men to women was 40/36, the age range was 14-81 years, and the average age was 37.70 years (SD 18.54); 78 patients were in the nonfever group, the ratio of men to women was 33/45, the age range was 14-87 years, and the average age was 38.76 years (SD 17.19). We also established a control group with 40 patients; the male to female ratio in this group was 19/21, the age range was 19-80 years, and the average age was 39.20 years (SD 19). Patients were excluded if they had high metabolism specific to head and face tissue (eg, tumors, infections), abnormally low metabolism (eg, benign nodules), or abnormal blood flow (eg, hemangioma).

Questionnaire

A questionnaire was developed according to the design of the study, including questions related to general personal and family information, previous medical history (tuberculosis, chronic bronchitis, asthma, hypertension, diabetes, etc), smoking history, drinking history, personal history, and the presence of acute upper respiratory tract infection within 1 year after physical examination.

Statistical Processing

SPSS 20.0 data analysis software (IBM Corporation) was used for single factor logistic regression analysis. The dependent variable (defined: l, not defined: 0) was whether an acute upper respiratory tract infection occurred, and each study factor used a single factor logistic regression equation as the independent variable. We selected variables with $P<.05$ as statistically significant, and a multiple unconditional logistic regression model was then fitted to the selected variables.

Experimental Method

An ATIR-M301B far-infrared thermal imager (China Chongqing Weilian Technology Co Ltd) and uncooled focal plane digital thermal imaging technology were used; the temperature resolution was 0.05 ℃, and the spatial resolution was 2 mrad. In the examination room without obvious air convection, the room temperature was controlled at 23 ±2 ℃. Before the inspection, the test site was exposed until the signs were stable and the skin temperature was appropriate. When the equilibrium temperature of the detection environment had been established for 5 to 15 minutes, the far-infrared thermal imager was used to collect far-infrared thermal images of the participant's head and face. The far-infrared thermal imager can scan and collect the infrared thermal energy emitted by the human body, and through computer analysis and processing, it can express different temperatures with different colors; therefore, it is an intuitive far-infrared thermal imaging system. By observing the

images, it is possible to accurately analyze changes in body surface temperature due to changes in the nervous system and analyze diseases. Diseases can be discovered at an early stage, and the changes and results of the disease can be observed in a timely fashion. Far-infrared thermal imaging has the characteristics of safety, convenience, and low cost. The images be checked repeatedly to dynamically observe changes in a patient's condition. The ambient temperature was 22 to 24 ℃, with no heat source interference, humidity of 50% to 60%, no strong light, and no wind. The instrument complies with national standards (GB/*t* 1965-2005). The instrument was equipped with a 320 × 240 uncooled focal plane infrared collection lens. The spectral response was 8 to 14 μm, the spatial resolution (instantaneous field of view) was 1.3 mrad, the temperature resolution was 0.05 ℃, and the acquisition speed was 30 frames/s. The thermal structure of the human body could be displayed objectively and digitally in the form of pseudocolor heat. All subjects were prepared in accordance with IRTI testing specifications before the test. During the test, the participant assumed the correct sitting posture and exposed the examination site, 2 meters away from the infrared lens, 1 faced vertically, 2 face up, and so on. Focusing, temperature calibration, image acquisition, storage, image processing, etc, were performed according to reference [55].

Qualitative Index of Infrared Thermal Image Evaluation

We observed the expression and distribution characteristics of the infrared thermal images. Different color scales represented different temperatures (white: super high temperature zone; red: high temperature zone; pink: hot zone; yellow: warm zone; green: cool zone; blue: low temperature zone; black: ultra-low temperature zone). Changes in color scale were compared between groups.

Quantitative Index of Infrared Thermal Image Evaluation

The average temperature corresponding to the extracted temperatures was quantitatively compared for the patients with upper acute respiratory infection with and without fever and the control group without fever on the left and right nasal areas and the left and right sides of the pharynx. For statistical processing, the data were extracted from the corresponding part of the infrared software system, and SPSS 20.0 was used to organize the data [56]. The measurement data were expressed as mean (standard deviation). We compared the average temperatures using analysis of variance.

Ethical Approval and Consent to Participate The experimental protocol was established according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Department of Pediatric Surgery, General Hospital Campus, the First Affiliated Hospital of Guangzhou Medical University. Written informed consent was obtained from individual participants or their guardians.
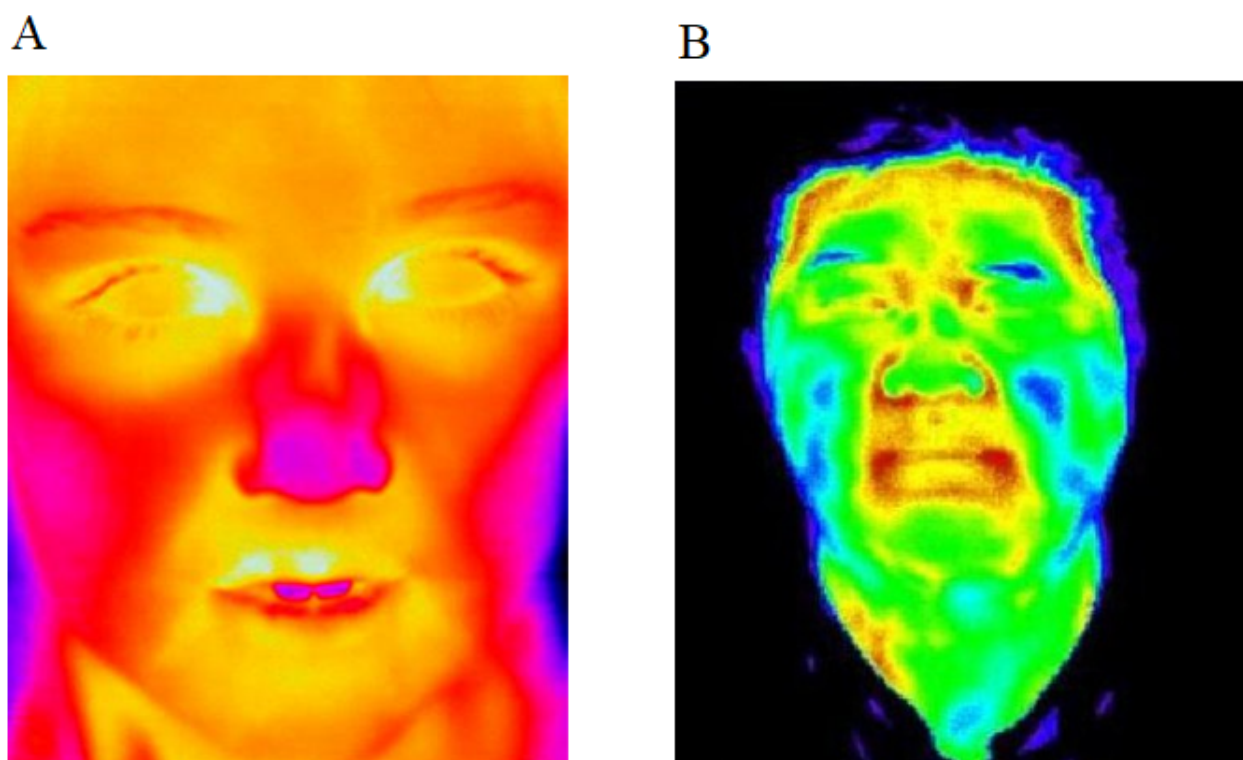
Results

Infrared Thermal Image Analysis

According to the statistical analysis of the data, as shown in the examples in Figure 1, the infrared thermograms of the patients in the nonfever group mainly showed "low temperature" blue or green color, the infrared expressions on the left and right sides have good symmetry, and the average temperature difference does not exceed 1 °C. The expression is similar, and the corresponding body surface area is a focal or large-scale focal or diffuse pink hot zone or red hot zone; this effect is more obvious in the fever group than in the nonfever group. Infrared temperature measurement technology avoids direct contact between the thermometer and the object and does not affect the temperature field distribution of the object; this can ensure high temperature measurement accuracy. A high-performance infrared thermometer can distinguish a temperature difference of 0.01 ºC.

Figure 1. Infrared thermograms of a patient in the fever group (left) and a patient in the nonfever group (right). Infrared thermal image distribution characteristics: white: ultra-high heat area; red: high heat area; pink: hot area; yellow: warm area; green: cool area; blue: cold area; black: ultra-cold area.

Quantitative Temperature Distribution and Comparison

According to the statistical analysis of the data, as shown in Table 1, the average temperature of the infrared thermal image of the corresponding body surface area of the nasal cavity and larynx in the fever group is higher than that in the nonfever group; however, the average body temperature of both groups is higher than that of the normal control group ($P=.003$).

Table 1. Quantitative distribution of temperature of the patients in the fever, nonfever, and control groups (N=194).

Group	n	Temperature (ºC), mean (SD)			
		Nasal region		Throat region	
		Left	Right	Left	Right
Fever	76	36.78 (0.67)	36.85 (0.72)	36.34 (0.66)	36.40 (0.68)
Nonfever	78	34.54 (0.47)	34.63 (0.49)	34.28 (0.53)	34.25 (0.56)
Control	40	33.28 (0.42)	33.37 (0.47)	33.09 (0.49)	33.14 (0.77)

Analysis of Acute Upper Respiratory Tract Infection

Gender Analysis

According to the statistical analysis of the data, as shown in Table 2, the incidence was 24.8% (82/331) for male patients and 13.9% (46/331) for female patients. There was a significant difference between men and women (*P*<.001).

Table 2. Analysis of incidence of respiratory infection by gender (n=331).

Gender	Acute upper respiratory tract infections, n	Nonrespiratory infections, n	Incidence rate (%)
Female	46	109	13.9
Male	82	94	24.8

Analysis of Related Factors

According to the statistical analysis of the data, shown in Figure 2, 128 cases of acute upper respiratory tract infection were observed in our study; the prevalence of upper respiratory tract infection by sex was 64.1% (82/128) males and 35.9% (46/128) females, while 68% (87/128) were smokers. It can be seen that smokers were more likely to have acute upper respiratory tract infection than nonsmokers (*P*<.001). At the same time, there was also a significant difference between men and women (*P*<.001). Of these patients, 57.8% (74/128) had hypertension. It can be seen that the incidence of acute upper respiratory tract infection in patients with hypertension was higher than that in patients without hypertension (*P*<.001). At the same time, there was no significant difference in the proportion of men and women with hypertension.

Figure 2. Prevalence of relevant factors among male patients, female patients, and all patients.
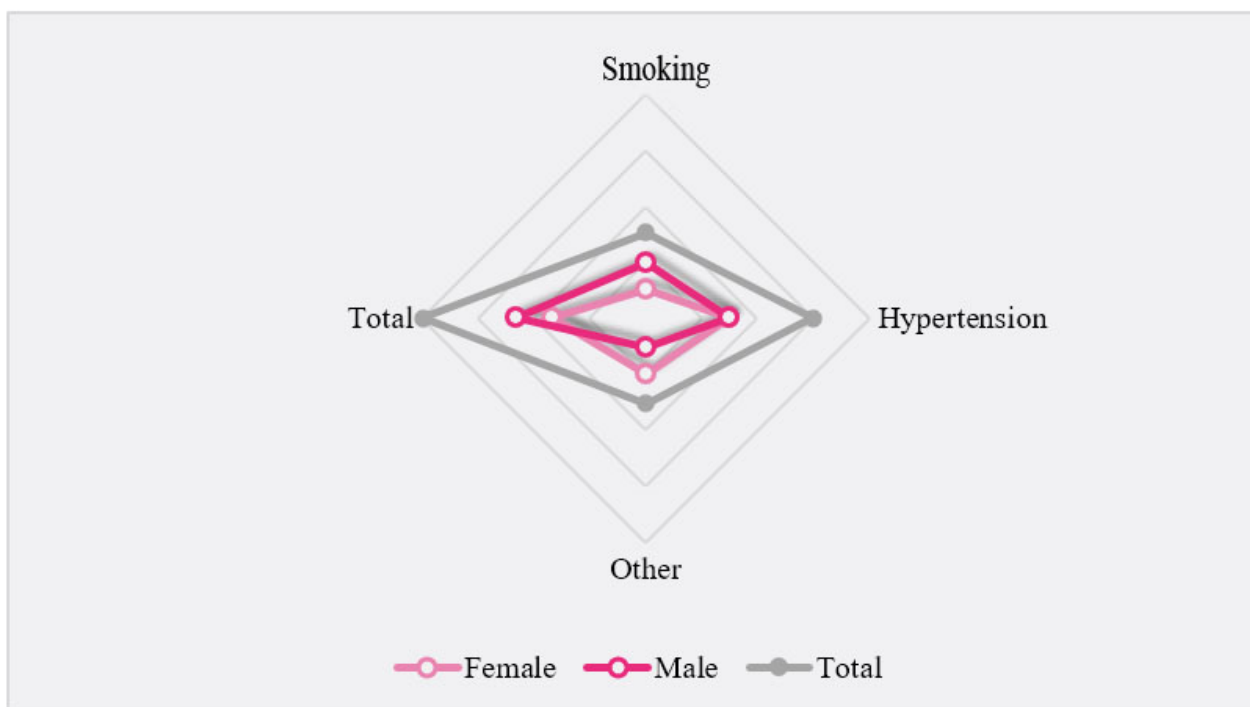
Discussion

Principal Findings

We found that that smokers are more likely to have acute upper respiratory tract infection than nonsmokers (*P*<.05), while men had a statistically higher prevalence of acute upper respiratory tract infection than women (*P*<.05). It is known that men smoke more than women [57]. Smoking is a risk factor for respiratory infection. First, the harmful substances in tobacco will destroy the immune monitoring cells in the airway (ie, phagocytes); thus, their phagocytic capacity and lethality will be reduced. Secondly, smoking can stimulate the proliferation of goblet cells; these cells secrete large amounts of mucus and fewer antibodies, which is conducive to the growth of bacteria. At the same time, smoking will destroy the cilia of the ciliated columnar epithelial cells of the respiratory tract, render them shorter, irregular, or incomplete, and prevent the smooth discharge of sputum [58].

Smoking can also directly stimulate the airway, cause airway spasms, and affect sputum drainage. The above adverse factors can weaken the defense ability of the respiratory tract, and the respiratory tract infection causes the damaged ciliated columnar epithelial cells to gradually develop into squamous epithelium. On the one hand, this weakens the purification ability of the airway; on the other hand, it also carries the risk of cancer. As an independent and serious risk factor of respiratory tract infection, smoking has attracted increasing attention in recent years. The most common respiratory diseases associated with smoking are lung cancer, bronchitis, and emphysema [59,60].

Conclusions

IRTI can provide an objective and quantifiable reference for the visual diagnosis of people with acute upper respiratory infection, and it can be used as one of the effective indicators of clinical diagnosis. There are obvious abnormal expressions of infrared thermography in the corresponding parts of the body surface.

The pathological features of acute sinusitis and acute pharyngitis are inflammatory changes with vascular exudation as the central link, and the local manifestation is elevated body temperature.

Because IRTI is highly sensitive to vascular disease or inflammation, infrared detection can show that the average temperature of the nasal cavity area and the middle neck throat area of the corresponding surface of acute sinusitis and acute pharyngitis is significantly higher, showing typical abnormal thermal images.

Conflicts of Interest

None declared.

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Abbreviations

IRTI: infrared thermal imaging
SARS: severe acute respiratory syndrome

Original Paper

Exploratory Analysis of Electronic Cigarette–Related Videos on YouTube: Observational Study

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Abstract

Background: Electronic cigarette (e-cigarette) use has become more popular than cigarette smoking, especially among youth. Social media platforms, including YouTube, are a popular means of sharing information about e-cigarette use (vaping).

Objective: This study aimed to characterize the content and user engagement of e-cigarette–related YouTube videos.

Methods: The top 400 YouTube search videos related to e-cigarettes were collected in January 2020. Among them, 340 valid videos were classified into provaping, vaping-warning, and neutral categories by hand coding. Additionally, the content of e-cigarette videos and their user engagement (including average views and likes) were analyzed and compared.

Results: While provaping videos were dominant among e-cigarette–related YouTube videos from 2007 to 2017, vaping-warning videos started to emerge in 2013 and became dominant between 2018 and 2019. Compared to vaping-warning videos, provaping videos had higher average daily views (1077 vs 822) but lower average daily likes (12 vs 15). Among 161 provaping videos, videos on user demonstration (n=100, 62.11%) were dominant, and videos on comparison with smoking had the highest user engagement (2522 average daily views and 28 average daily likes). Conversely, among 141 vaping-warning videos, videos on potential health risks were the most popular topic (n=57, 40.42%) with the highest user engagement (1609 average daily views and 33 average daily likes).

Conclusions: YouTube was dominated by provaping videos, with the majority of videos on user demonstrations before 2018. The vaping-warning videos became dominant between 2018 and 2019, with videos on potential health risks being the most popular topic. This study provides updated surveillance on e-cigarette–related YouTube videos and some important guidance on associated social media regulations.

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Introduction

Electronic cigarette (e-cigarette) use has increased significantly since its introduction in the US market in 2007, especially among youths [1,2]. Although the prevalence of e-cigarette use in youths decreased in 2020 compared to 2019, 19.6% of high school students and 4.7% of middle school students still reported using e-cigarettes [3,4]. The long-term health risks of e-cigarette use are still unclear; however, e-cigarette use has been associated with many health problems, including respiratory disorders [5-8], cardiovascular disease [9-11], and potential mental and cognitive problems [12,13].

e-Cigarettes are often marketed as healthier alternatives to cigarette smoking by e-cigarette companies on the internet [14,15]. People interested in e-cigarettes might seek further information about the product and its use on the internet,

especially on social media [16,17]. Social media, such as Twitter, Instagram, and YouTube, have become a popular platform for e-cigarette users to share their experiences and for vaping companies to promote their products. Apparently, Twitter is dominated by tweets promoting e-cigarettes [18,19]; the e-cigarette–promoting posts have higher user engagement than e-cigarette–warning posts on Instagram [20]. Therefore, e-cigarette companies aggressively promote their products to the public, especially youth, through social media.

YouTube, created in 2005, is a popular social media platform with over 2 billion users and over billions of views daily [21]. YouTube was initially designed and created for sharing videos, but e-cigarette companies have used it extensively to promote tobacco products (including e-cigarettes) [22,23]. Many YouTube videos, especially on e-cigarettes, do not have an age restriction [24], making their promotional content on tobacco products easily accessible by youths, affecting their perception of tobacco products and causing major public health implications. As a result, YouTube has been promoting tobacco products, including e-cigarettes [25,26]; e-cigarette promotional videos were the dominant e-cigarette–related YouTube videos in 2012-2013 [24].

Social media such as YouTube has been widely used for sharing information and communicating with others. It is a rich data source for public health professionals to understand what e-cigarettes–related information is posted on YouTube and how they get disseminated, thus providing important information for public health surveillance. With the rapid increase of e-cigarette use in recent years, especially among youth, e-cigarette–related YouTube videos may have evolved. Therefore, it is important to examine more recent e-cigarette–related videos on YouTube to study the dynamic changes in such videos. Additionally, it is crucial to examine the user engagement of different e-cigarettes–related videos for some effective guidance on stopping the current vaping epidemic. This study aimed to characterize the e-cigarette–related YouTube videos by identifying provaping and vaping-warning videos and comparing their content and user engagement. Results from the study could help us understand what information related to e-cigarettes has been posted on YouTube and provide potential effective approaches to protect public health, especially among youths.

Methods

Data Collection

e-Cigarette–related videos and their associated metadata were downloaded from YouTube on January 12, 2020, with the search keyword "e-cigarette" using youtube-dl (a command-line program). Top search videos were selected based on their presence in the search, which might be more likely to be viewed by users. Out of the top 400 YouTube videos related to e-cigarettes, only 373 videos were successfully downloaded from YouTube. Among them, 20 videos were not in English, and 13 videos were uploaded after 2019. Finally, we obtained 340 unique e-cigarettes–related videos posted on YouTube between 2007 and 2019 and used them for further analysis.

We downloaded the metadata associated with each YouTube video, including video duration time (seconds), age limit, number of views, number of likes, and the posted date. Based on the posted date, we calculated the number of posted days for each video. To better compare the user engagement among different video categories, we normalized the number of views and likes to the number of posted days on YouTube for each video. The differences in user engagement measures (such as the number of likes and views) were tested by the two-sample t test at a significance level of .05 using the statistical analysis software R, version 4.0.3 (R Core Team).

Video Hand Coding

To hand code the videos, 2 reviewers watched each downloaded e-cigarette–related YouTube video. The content of each video was summarized after watching it carefully. Each video was categorized as provaping, vaping-warning, or neutral based on its overall attitude toward e-cigarettes. A provaping video was defined as promoting e-cigarette use, such as showing certain e-cigarette products, vaping demonstrations, and the benefits of vaping. A vaping-warning video was defined as discouraging e-cigarette use, such as presenting the potential health risks of vaping and policies regulating e-cigarettes. Neutral videos did not clearly express either provaping or vaping-warning messages, such as explaining why e-cigarettes are popular or discussing their pros and cons.

Each video was categorized further based on its video content. Provaping videos were categorized as (1) user demonstration: showing how to use e-cigarettes and vaping tricks; (2) comparison with smoking: emphasizing that e-cigarettes were healthier and safer than smoking and can help quit smoking or replace cigarettes; (3) introduction of e-cigarettes: providing an introduction to e-cigarettes and available flavors; (4) reduced health risks: highlighting the reduced known (such as lung and respiratory) or unknown health problems; (5) product sale: including brand introduction and web links to purchase or obtain coupon; and (6) promoting e-cigarettes: underlining cost-savings, use of e-cigarettes anywhere, and the experience resembling that of real cigarettes.

Vaping-warning videos were categorized as (1) e-cigarette regulation: including vaping ban, legal fight against e-cigarettes, and the Food and Drug Administration (FDA) regulation; (2) comparison with smoking: arguing against healthier- and safer-than-smoking messages or unproven efficacy for quitting cigarettes; (3) potential health risks: showing known and unknown health risks, lung or blood problem, respiratory symptoms; (4) explosion hazard: describing accidents due to e-device explosion; and (5) youth addiction: including nicotine addiction in youth or role as a gateway drug.

The agreement between the 2 independent reviewers on attitude toward e-cigarettes was 87.43%, while the agreement on video content was 78.07%. Any discrepancy between the 2 reviewers was resolved by discussion among the 4-member research team.

Results

e-Cigarette–Related YouTube Videos

Among 340 e-cigarettes–related YouTube videos, 141 (41.5%) were vaping-warning videos, 161 (47.3%) were provaping videos, and 38 (11.2%) were neutral videos without any evident attitude toward e-cigarettes.

The videos shortlisted for the study were posted on YouTube between 2007 and 2019 (Figure 1). Beginning with 2007, the number of provaping videos kept increasing until 2013 and then significantly decreased in 2014. In contrast, the number of vaping-warning videos started increasing in 2013 and surged drastically in 2019. Neutral videos maintained a low level but exhibited a slight increase recently.

Figure 1. The popularity of e-cigarette videos on YouTube over time.
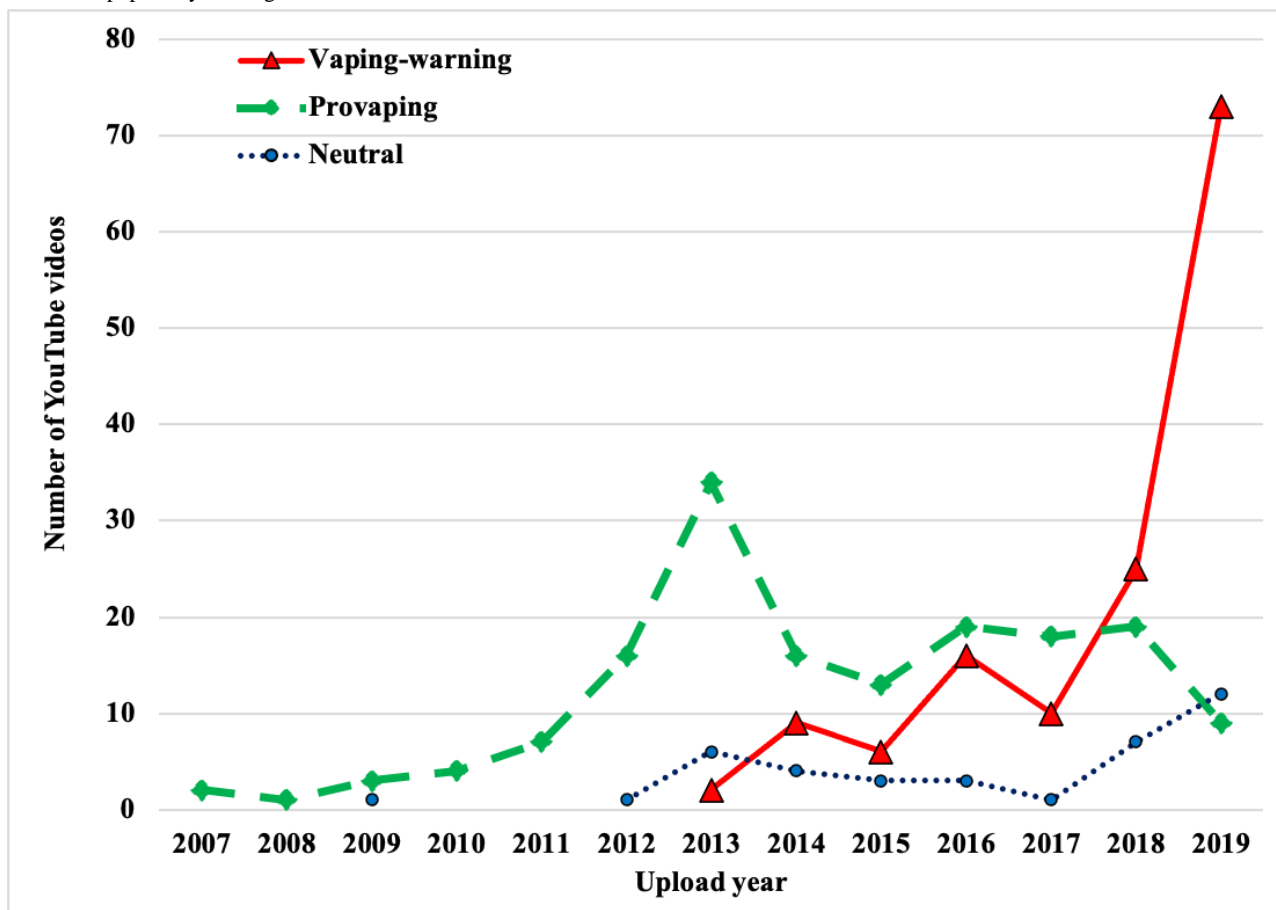
As shown in Table 1, we compared user engagement measures among different types of e-cigarette–related YouTube videos. Provaping videos were found to have a higher number of average views (778,569 vs 380,671, *P*=.24) and likes (7300 vs 5523, *P*=.70) than vaping-warning videos. Since the posted date for each video on YouTube was different (from 2007 to 2019), the number of days for each video posted on YouTube was also different. For example, the average number of posted days for provaping videos was 1806 days, whereas it was 605 days for vaping-warning videos. The average number of daily views for provaping videos was higher than that for vaping-warning videos (1077 vs 822, *P*=.72), but the average number of daily likes for provaping videos was lower than that for vaping-warning videos (12 vs 15, *P*=.85). The vaping-warning videos had a longer video duration (759.5 seconds vs 370.8 seconds) on average than provaping videos. The average number of daily views and likes for neutral videos was between the average daily views and likes for provaping and vaping-warning videos.

Table 1. Characteristics of e-cigarette–related YouTube videos.

Video categories	Videos, n	Views, mean (SE)	Likes, mean (SE)	Daily views, mean (SE)	Daily likes, mean (SE)	Posted days, mean (SE)	Video duration (seconds), mean (SE)
Vaping-warning	141	380,671 (166,961)	5523 (3444)	822 (527)	15 (12)	605 (55)	759.5 (134)
Neutral	38	251,231 (89,292)	2732 (1276)	506 (278)	14 (11)	1128 (159)	561.1 (159)
Provaping	161	778,569 (293,749)	7300 (3014)	1077 (493)	12 (6)	1806 (76)	370.8 (26)

Provaping YouTube Videos

Among 161 provaping YouTube videos (Table 2), most (n=100, 62.11%) focused on user demonstration by showing how to use e-cigarettes and some vaping techniques, followed by product sale (n=25, 15.53%), and comparison with smoking (n=16, 9.94%). Among provaping videos, the videos that compared e-cigarettes with smoking had the highest number of views (2,121,410 views/video) and likes (21,512 likes/video) on average.

Table 2. Characteristics of provaping YouTube videos.

Topics	Videos, n (%)	Views, mean (SE)	Likes, mean (SE)	Daily views, mean (SE)	Daily likes, mean (SE)	Posted days, mean (SE)
Comparison with smoking	16 (9.94)	2,121,410 (978,736)	21,512 (9237)	2522 (1195)	28 (12)	1109 (214)
Introduction of e-cigarettes	8 (4.97)	225,026 (85,275)	3040 (1728)	165 (72)	3 (2)	1680 (427)
Reduced health risks	5 (3.11)	53,877 (38,799)	835 (726)	401 (386)	7 (7)	937 (441)
Product sale	25 (15.53)	96,232 (34,949)	686 (380)	113 (59)	1 (0)	1806 (154)
Promoting e-cigarettes	7 (4.35)	183,037 (128,176)	1429 (1237)	48 (29)	0 (0)	3260 (382)
User demonstration	100 (62.11)	856,504 (442,943)	7629 (4570)	1266 (767)	15 (10)	1869 (89)

Videos on user demonstration had the second highest number of views (856,504 views/video) and likes (7629 likes/video), followed by videos introducing e-cigarettes (225,026 views/video and 3040 likes/video) and promoting e-cigarettes (183,037 views/video and 1429 likes/video). After normalizing the number of views and likes to the number of posted days for each video, as shown in Table 2, the videos that compared e-cigarettes with smoking had the highest number of daily views (2522 daily views/video) and likes (28 daily likes/video), followed by user demonstration (1266 daily views/video and 15 daily likes/video), and reduced health risks (401 daily views/video and 7 daily likes/video).

Vaping-Warning YouTube Videos

Among 141 vaping-warning YouTube videos, there were 57 (40.42%) videos on the potential health risks of e-cigarettes, 33 (23.40%) videos talking about e-cigarette regulation, and 25 (17.73%) videos showing exploded e-cigarette devices (Table 3).

Table 3. Characteristics of vaping-warning YouTube videos.

Topics	Videos, n (%)	Views, mean (SE)	Likes, mean (SE)	Daily views, mean (SE)	Daily likes, mean (SE)	Posted days, mean (SE)
Comparison with smoking	4 (2.84)	97,747 (71,649)	845 (638)	91 (35)	1 (0)	885 (425)
e-Cigarette regulation	33 (23.40)	35,853 (10,919)	566 (293)	256 (67)	3 (1)	173 (38)
Explosion hazard	25 (17.73)	326,335 (166,201)	1861 (1010)	243 (86)	1 (1)	1016 (113)
Potential health risks	57 (40.42)	595,728 (386,188)	10,802 (8400)	1609 (1299)	33 (29)	571 (88)
Youth addiction	22 (15.60)	453,889 (330,220)	4621 (3334)	423 (218)	4 (2)	823 (141)

Compared to other video types, videos about the potential health risks had a higher number of views (595,728 views/video) and likes (10,802 likes/video) on average. Videos showing youth addiction to e-cigarettes also had high views (453,889 views/video) and likes (4621 likes/video). After normalizing the number of days posted on YouTube, the videos about the potential health risks of e-cigarettes had the highest number of daily views (1609 daily views/video) and likes (33 daily likes/video), followed by videos on youth addiction (423 daily views/video and 4 daily likes/video).

Discussion

Principal Findings

In this study, we characterized the top 340 searches for e-cigarette–related videos on YouTube. While provaping videos were more prevalent before 2018, vaping-warning videos became dominant more recently (2018-2019). Additionally, the provaping videos had higher average daily views than the vaping-warning videos; the vaping-warning videos had relatively higher average daily likes than the provaping videos. Among the provaping videos, the majority were about user demonstration, which had relatively more daily views and likes on average than other video types except for the videos on comparison with smoking. Among the vaping-warning videos, the videos showing the potential health risks of e-cigarettes were the most prevalent, and they also had the most user engagement (daily views and likes).

Within the study time frame starting 2007, the number of provaping videos posted on YouTube increased continuously, reaching a peak in 2013, and then dropped significantly in 2014. In contrast, the number of vaping-warning videos recorded a continuous increase from 2013 and reached a significantly high level in 2019. On April 25, 2014, the FDA published a long-awaited proposed rule that put e-cigarettes under FDA regulation like other tobacco products [27]. Whether the FDA rule played a role in the dramatic decrease of provaping videos in 2014 needs further investigation in future studies.

Several studies have shown that YouTube has been used unevenly for promoting e-cigarettes in 2013 and 2014 [23,24,28,29]. In this study, we showed that provaping videos were dominant on YouTube before 2018, especially before 2014, which is consistent with the previous findings. An earlier study examined the total number of views for different e-cigarette–related YouTube videos; however, it did not calculate the average number of views for different types of videos and did not compare the user engagement among different videos [24]. This study examined the average number of views and likes for each type of video and calculated the average number of daily views and likes, reflecting user engagement on these videos. This study compared the three video categories and observed that the provaping videos had higher views and likes than the vaping-warning videos, consistent with the findings from a previous study [23]. Among provaping videos, about 10% of videos comparing e-cigarettes with smoking (mainly, vaping is a safer alternative to smoking) had the most user engagement (2522 daily views and 28 daily likes). Thus, there is some evidence that promoting e-cigarette as a safer alternative could influence its usage [30]. Furthermore, over 62% of provaping videos were about user demonstration and had a relatively high user engagement (average daily views and likes). Previous studies showed that product advertisement and user sharing related to e-cigarettes were the top genres on YouTube [23]. All e-cigarette–related YouTube videos collected in this study did not have an age restriction, suggesting that all YouTube users, including youth, could access these videos. Therefore, these provaping videos might have a great potential to promote e-cigarette use and might be partially responsible for the e-cigarette epidemic, especially among youth in recent years. Considering their prevalence on YouTube and high user engagement, these provaping videos should have an age verification system in place to prevent youth access.

Our study showed that among the 340 YouTube videos analyzed, the vaping-warning YouTube videos became dominant starting in 2018 and surged dramatically in 2019, correlating well with the EVALI (e-cigarette or vaping product use associated lung injury) epidemic in the United States [31]. Nearly half of YouTube videos in 2015 were educational, medical, or news videos [32]. Among vaping-warning videos, the videos on the potential health risks of e-cigarette use were the most prevalent and had the highest user engagement, providing a potentially effective way to inform the public, especially youth, about the health risks of e-cigarette use and protect public health. Therefore, these vaping-warning videos, especially those about the potential health risks of e-cigarette use, should be encouraged by public health authorities. The dominance of vaping-warning videos on YouTube in 2019 might contribute to the decrease of e-cigarette use, especially among youth in 2020 [3].

Limitations

This study has several limitations. First, we collected only the top 400 searches for e-cigarette–related YouTube videos in the English language using the keyword "e-cigarette," which might not represent the whole picture and introduce some potential biases in our results. In the future, other relevant keywords (such as "vaping" and "JUUL") could be included to collect more e-cigarette–related YouTube videos for further analyses. Second, since there was no demographic information about the users (such as age and gender) available from YouTube, we did not know who watched these videos. Therefore, we could not determine the impact of these e-cigarette videos on different demographic groups. Third, this study's relatively small sample size resulted in large variations and insignificant differences among different videos in terms of user engagement. Fourth, we did not segment each video in this study, possibly affecting the coding accuracy. Fifth, our content analysis was based on 340 videos only, and it is possible that there were other e-cigarette–related videos that could not be covered by our current categories. Sixth, this study examined the user engagement of each video type, which could be affected by the characteristics (number of subscribers and number of posted videos) of user accounts who posted these videos, especially the characteristics of those influencers. Therefore, it is important to understand how these features can affect the user engagement of e-cigarette–related videos in future studies. Finally, this study did not consider differences in geographic locations as YouTube is an international platform; however, different geographical locations and their impacts in different countries could be pursued in future studies.

Conclusions

The study showed that e-cigarette–related YouTube videos were initially dominated by provaping videos and then vaping-warning videos, demonstrating the importance of such surveillance on YouTube to understand the dynamic changes in e-cigarette–related videos. Additionally, we showed different user engagement metrics for different e-cigarette videos on YouTube, providing important information for public health authorities to aid in developing appropriate regulations on social media to protect public health, especially among youth.

Authors' Contributions

ZX and DL conceived and designed the study. XW, YG, and ZX analyzed the data. ZX wrote the manuscript. XW, YG, ZX, and DL assisted with the interpretation of analyses and edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

e-Cigarette: electronic cigarette
EVALI: e-cigarette or vaping product use associated lung injury
FDA: Food and Drug Administration

Original Paper

Overview of Graves Ophthalmopathy Literature From 1999 to 2019: Bibliometric Analysis

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Abstract

Background: Research on Graves ophthalmopathy has increased remarkably over the last 2 decades; however, few statistical analyses of the data presented in these publications have been conducted.

Objective: This study aims to detect and analyze emerging trends and collaboration networks in Graves ophthalmopathy research.

Methods: Graves ophthalmopathy–related publications from 1999 to 2019 were collected from the Web of Science Core Collection Database. Collected publications were restricted by category (article or review) and language (English). Bibliometric analyses included changes in the annual numbers of publications, journals, authors, countries, institutions, keywords, and references.

Results: In total, 3051 publications that met the criteria were collected. The number of annual publications has exhibited an increasing trend over the last 20 years. The journal *Thyroid* ranked first, publishing 183 Graves ophthalmopathy–related studies. There was no evidence of a relationship between impact factor (IF) and the number of publications (P=.69). The author Smith TJ had the largest number of publications on Graves ophthalmopathy (n=83). Of the countries that had published Graves ophthalmopathy–related articles, the United States had the largest number (n=784) and the highest centrality (0.18). Among institutions, the University of Pisa (Italy) contributed the most Graves ophthalmopathy–related articles (n=114). The most recent burst keywords (proliferation, rituximab, and selenium) and references may provide clues on emerging trends in research and clinical practice.

Conclusions: This bibliometric analysis highlights countries, institutions, and authors who contributed to Graves ophthalmopathy–related publications. Emerging trends in Graves ophthalmopathy research, based on burst keywords and references, may provide clues relevant to clinical practice and future research.

KEYWORDS

Introduction

Graves Ophthalmopathy

Graves ophthalmopathy is an organ-specific autoimmune disease related to Graves disease (GD), which is among the most frequent extrathyroid manifestations of this condition [1]. The most common clinical features of Graves ophthalmopathy are eyelid retraction and exophthalmos, with incidence rates of 90% and 62%, respectively [2]. Other manifestations of Graves ophthalmopathy include restrictive extraocular myopathy, exposure keratitis, and optic nerve dysfunction. The pathogenesis of Graves ophthalmopathy is unclear, with numerous issues yet to be resolved. Recently, orbital fibroblasts have been proposed to play an important role in adipogenesis

and fibrosis. In vivo, orbital fibroblasts differentiate into adipocytes and myofibroblasts in response to peroxisome proliferator-activated receptor-γ and transforming growth factor β, respectively, and these are the main pathological changes in the inactive stage of Graves ophthalmopathy [3]. Recommended first-line therapeutic strategies include glucocorticoid and thyroid function control [4]. Many new therapeutic strategies for Graves ophthalmopathy have recently emerged, including teprotumumab, which can reduce the degree of exophthalmos [5]. Given the numerous Graves ophthalmopathy–related publications, it is important to analyze these research studies to provide an overview of the field. Although some previous reports have introduced state-of-the-art bibliometric analysis of related diseases, these publications also included other conditions and did not provide an accurate description of the single disease, Graves ophthalmopathy [6,7]. Furthermore, other bibliometric analyses of eye-related diseases, such as diabetic retinopathy and glaucoma, have been reported; however, bibliometric data related to thyroid-associated ophthalmopathy are lacking [8,9].

Bibliometric Analyses

Systematic reviews, meta-analyses, and bibliometric analyses can be used to describe developments in a specific field. Systematic reviews and meta-analyses are primarily used to compare the effectiveness or side effects of treatment strategies or drugs and can provide decisive or suggestive data; however, they do not provide descriptive statistical analysis of research in a field [10]. Bibliometric analysis is a statistical analysis approach that can be used to describe the characteristics of large-scale data and determine the main development trends based on the results of database searches on a given topic [11]. Through bibliometric analysis, data on the number of publications, countries, institutions, authors, and research hotspots are extracted, providing visual results describing research status [12]. Bibliometric analysis is a quantitative and visual process that includes the detection, description, evaluation, and monitoring of published research studies [13]. CiteSpace 5.6R5 (32-bit) is a bibliometric analysis tool developed by Chaomei Chen in 2004 and has been used by many researchers [13]. For example, CiteSpace has been used to analyze the development and trends in research on valvular heart disease [14]. In our study, CiteSpace was the main bibliometric analysis tool used.

Destination

In this research, we aim to analyze the characteristics of Graves ophthalmopathy research and assess the tendencies and perspectives related to Graves ophthalmopathy over the past 20 years, from 1999 to 2019.

Methods

Data Sources and Search Strategies

The Web of Science database is a collection of multidisciplinary academic journals and an authoritative citation information source that serves as a primary scientific database for many researchers [15]. The data source for this study was the Web of Science Core Collection (WoSCC) database, which includes

the following sources: Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index, Conference Proceedings Citation Index-Science, Conference Proceedings Citation Index-Social Science & Humanities, Emerging Sources Citation Index, and Current Chemical Reactions [15]. The research strategies were topic search, that is, *Graves ophthalmopathy* OR *Graves orbitopathy* OR *thyroid-associated ophthalmopathy* OR *thyroid eye disease*, over the period 1999-2019. On July 21, 2020, a total of 3848 records were obtained. After restricting the document type to article and review and language to English, 3051 records remained (Multimedia Appendix 1).

Data Collection and Preprocessing

All records and references were saved with a name in the format *download_**.txt*, as this format is recognized by CiteSpace [16]. Data from publications collected from WoSCC were saved in documents, including title, authors, countries, institutions, abstracts, keywords, journal, and publication date. After the removal of duplicates using CiteSpace, records were classified by year. As the same author name could be presented in two or three forms (eg, *TJ Smith* or *Terry J Smith*), we replaced different forms found with 1 form in the raw data before detecting the cooperating relationships among authors. Country and institution names were not preprocessed, as they had only single names in the raw data.

Bibliometric Analysis

We used CiteSpace 5.6R5 (32-bit). Preprocessed data were uploaded to CiteSpace, and bibliometric analysis was performed according to the information included in the data documents [13]. Network maps visualizing collaborations among journals, authors, countries, and institutions were generated. In network maps, points represent an author, country, or institution, and lines represent relationships between points. Larger points and stronger lines represent more records and stronger collaboration relationships, respectively [11]. Burst detection analysis of keywords and references was used to discern trends, outlooks, and research interests [17]. Time slicing was conducted from January 1999 to December 2019, with 1 year per slice. Default selection criteria parameters were used, including the *pruning* parameters, *pathfinder* and *pruning sliced networks*, and *visualization* parameters, *cluster view-static*, and *show merged network*.

Centrality, also referred to as betweenness centrality, is an index that can be used to illustrate the importance of a node in a network [13]. In CiteSpace, centrality can be used to identify turning points and measure the co-operation and participation of countries in literature production. Higher centrality values indicate closer co-operation relationships of a country with others, a higher degree of participation, and a greater impact if deleted [18]. Centrality was calculated using the following equation:

where g_{st} represents the number of shortest paths from node s to node t and n^{i}_{st} represents the number of shortest paths that pass through node i in g_{st}.

GraphPad Prism 8 and web-based bibliometric analysis platforms were used to analyze annual publication outputs and count numbers of publications according to journal. Oracle Crystal Ball (11.1.2.4.400) was used to predict the trend in the numbers of publications. Furthermore, Hirsch index (H-index) values were searched from the Web of Science; H-index values indicate that researchers have published h papers and that each paper was cited at least h times and can be used to describe the cumulative impact of an author, country, or institution [19]. Journal IFs were obtained from the 2019 version of Journal Citation Reports, which are used as a measure of the scientific value of research [20]. IBM SPSS Statistics 24 was used to create fitting curves for the number of publications and analyze relationships between IF and numbers of Graves ophthalmopathy–related publications in journals. SPSS 24 was also used for hypothesis testing.

Results

Publication Outputs

Searching the Web of Science database using the search conditions described earlier yielded 3051 records that met the criteria that were included in further analysis. The distribution of Graves ophthalmopathy–related publication numbers annually from 1999 to 2019 is shown in Figure 1. The total number of publications increased from 89 in 1999 to 253 in 2019. The largest number of Graves ophthalmopathy–related publications over the past 20 years (1999–2019) occurred in 2018 (n=260). The number of publication outputs decreased in 2001, 2003, 2009, and 2013. An exponential fitting curve was generated using SPSS 24 (R^2=0.86; P<.001; Figure 1), which showed a significant increase in the number of publications over the last two decades. Furthermore, according to the exponential fitting curve, the number of outputs is predicted to continue increasing over the next 5 years, and the probability of increase is 92.8% according to the Oracle Crystal Ball.

Figure 1. Number of Graves ophthalmology–related publications from 1999 to 2019.
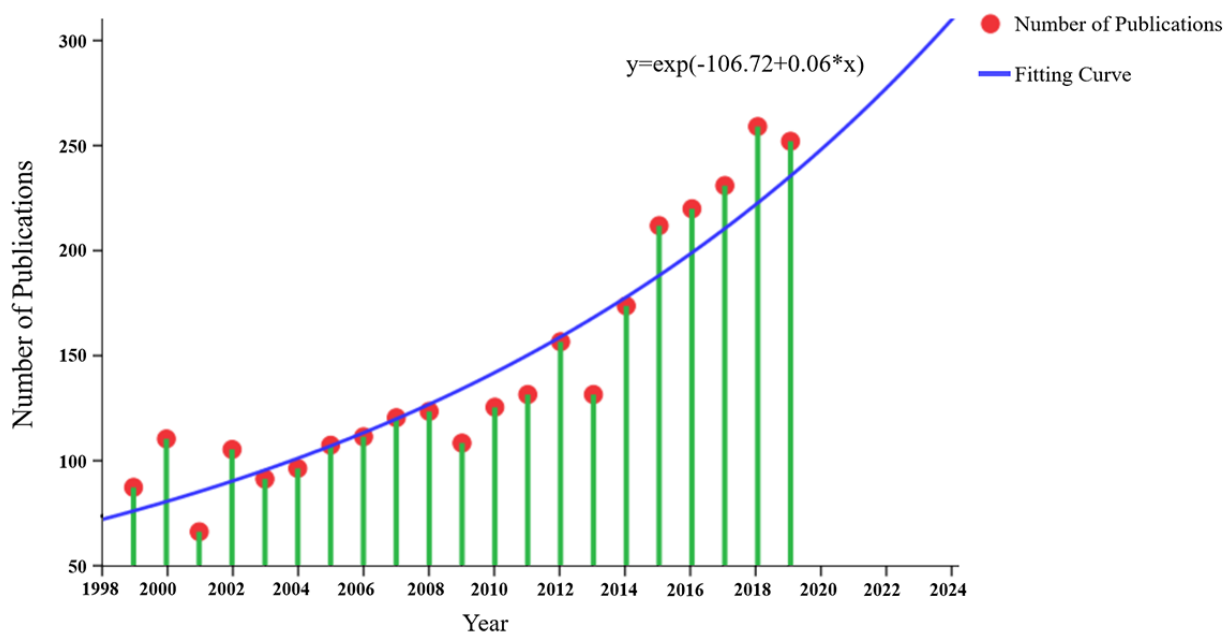
Distribution of Graves Ophthalmopathy–Related Publications in Journals

Information about journals from the Web of Science was analyzed to determine rank information. The 3051 identified publications were published in 691 journals. The top 10 journals with the highest number of publications are listed in Table 1. The total number of publications in these 10 journals was 929, which accounted for 30.44% (929/3051) of all publications. The number of publications in the top 10 journals ranged from 50 to 183. The journal *Thyroid* contributed the highest proportion of publications (n=183) among all the journals included in this research, followed by *Ophthalmic Plastic and*

Reconstructive Surgery (n=153) and *Journal of Clinical Endocrinology & Metabolism* (n=136). Furthermore, the *Journal of Clinical Endocrinology & Metabolism* had the highest total and mean number of citations. The 2019 IF of the top 10 journals ranged from 1.113 to 8.470, and 8 journals had an IF >3 and published 828 (27.1%) of the 3051 Graves ophthalmopathy–related papers from 1999 to 2019. The relationship between IF and the number of publications in the top 10 journals was assessed by Pearson correlation analysis in SPSS.22, which revealed no significant correlation (R^2=–0.145; P=.69). These data demonstrate that publishing papers in journals with a high IF remains challenging.

Table 1. Top 10 journals with the most published articles.

Rank	Journal	Impact factor (2019)	Publications, n (%)	Total number of citations	Mean number of citations
1	Thyroid	5.227	183 (6)	2500	13.66
2	Ophthalmic Plastic and Reconstructive Surgery	1.133	153 (5.01)	956	6.25
3	Journal of Clinical Endocrinology & Metabolism	5.339	136 (4.46)	3995	29.38
4	European Journal of Endocrinology	5.308	77 (2.52)	1552	20.16
5	Clinical Endocrinology	3.380	76 (2.49)	1402	18.45
6	Journal of Endocrinological Investigation	3.397	75 (2.46)	859	11.45
7	Eye	2.455	68 (2.22)	511	7.51
8	Investigative Ophthalmology & Visual Science	3.470	60 (1.97)	619	10.32
9	British Journal of Ophthalmology	3.611	51 (1.67)	761	14.92
10	Ophthalmology	8.470	50 (1.61)	796	15.92

Distribution by Author

A total of 9660 authors contributed to the studies included in this research. Co-operation relationships among authors were analyzed using the coauthor tool in CiteSpace. Co-operation among authors was visualized as a network map to illustrate potential partnerships (Figure 2). Co-operation relationships are represented by connections between nodes, with thicker connections indicating closer co-operation. The node size represents the number of author outputs, with larger size indicating more outputs. The top 10 authors with the largest number of Graves ophthalmopathy research publication outputs are presented in Table 2, and the data came directly from the Web of Science on August 4, 2020. Among the top 10 authors, Smith TJ had the largest number of articles (83/3051, 2.72%), followed by Marcocci C (73/3051, 2.42%) and Kahaly GJ (68/3051, 2.23%). Wiersinga WM (H-index=75) had the highest H-index among the top 10 authors, followed by Bartalena L (H-index=61), Marcocci C (H-index=60), and Hegedus L (H-index=60). The assessment of relationships between author and H-index by Spearman rank correlation in SPSS 24 detected no significant relationships (P=.38), possibly indicating that the number of author outputs is not an important factor influencing the H-index.

Figure 2. Network of co-operation relationships among authors generated using CiteSpace.

Table 2. Top 10 authors of the most articles.

Rank	Author	Publications	Percentage of 3051	H-index
1	Terry J Smith	83	2.72	54
2	Claudio Marcocci	73	2.4	60
3	George J Kahaly	68	2.2	46
4	Wilmar M Wiersinga	62	2.0	75
5	MicheleI Marino	55	1.8	26
6	Luigi Bartalena	53	1.7	61
7	Jin Sook Yoon	46	1.5	20
8	Mario Salvi	42	1.4	33
9	Raymond S Douglas	40	1.3	24
10	Laszlo Hegedus	39	1.3	60

Distribution by Country

The 3051 outputs included in this study originated from 83 countries or regions. In data preprocessing, we included data from Taiwan (78 publications) into those from China. The number of countries involved in the outputs and their distribution were analyzed using web-based bibliometric analysis platforms, and the results are shown in Figure 3. Different colors represent different countries, and the length of bars indicates the number of articles, where longer bars indicate a higher number of publications. The co-operation relationships are shown in Figure 4. Circles represent centrality, with wider circles representing

higher centrality. Connections between nodes represent co-operation between the countries. Detailed publication information for the top 10 countries is presented in Table 3. Among the top 10 countries, the United States had the most publications (784/3051, 25.69%), followed by China (350/3051, 11.47%) and Italy (301/3051, 9.87%). Furthermore, the United States had the largest centrality (0.18), followed by England (0.15) and Turkey (0.09), demonstrating that the United States had the highest level of co-operation with other countries. Moreover, country centrality was not significantly associated with the number of outputs from the country (Spearman rank correlation, P=.59).

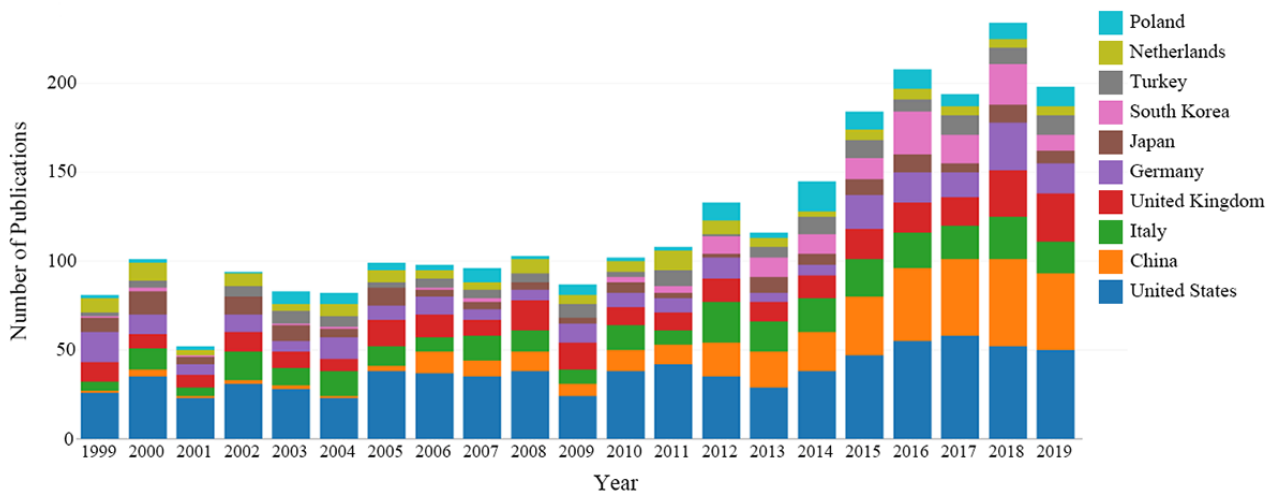**Figure 3.** Annual publications distributed according to country.

Figure 4. Network of co-operation among countries generated using the CiteSpace web-based analysis platform.

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Table 3. Top 10 countries with the most articles.

Rank	Country	Publications	Percentage of 3051	Centrality
1	United States	784	25.7	0.18
2	China	350	11.5	0.00
3	Italy	301	9.9	0.00
4	Germany	240	7.9	0.00
5	England	235	7.7	0.15
6	Japan	141	4.6	0.04
7	South Korea	134	4.4	0.04
8	Turkey	129	4.2	0.09
9	Netherlands	128	4.2	0.07
10	Poland	127	4.2	0.05

Distribution by Institution

A total of 2620 institutions contributed to 3051 publications on Graves ophthalmopathy research. The co-operation relationships among institutions are shown in Figure 5, and the top 10 institutions according to the number of publication outputs are presented in Table 4. Among the top 10 institutions, the University of Pisa ranked first with 114 publications, followed by the University of California, Los Angeles (n=91), and the University of Amsterdam (n=72). Of the top 10 institutions, 3 were in the United States and 2 in Italy, suggesting that these organizations made outstanding contributions to the field. Interestingly, the number of institutions in a country was proportional to the number of literature outputs (Spearman rank correlation, $r=0.77$; $P=.005$), demonstrating that the achievements of countries could not be attributed to specific institutions and that more institutions should be constructed to contribute to progress in the field of Graves ophthalmopathy research.
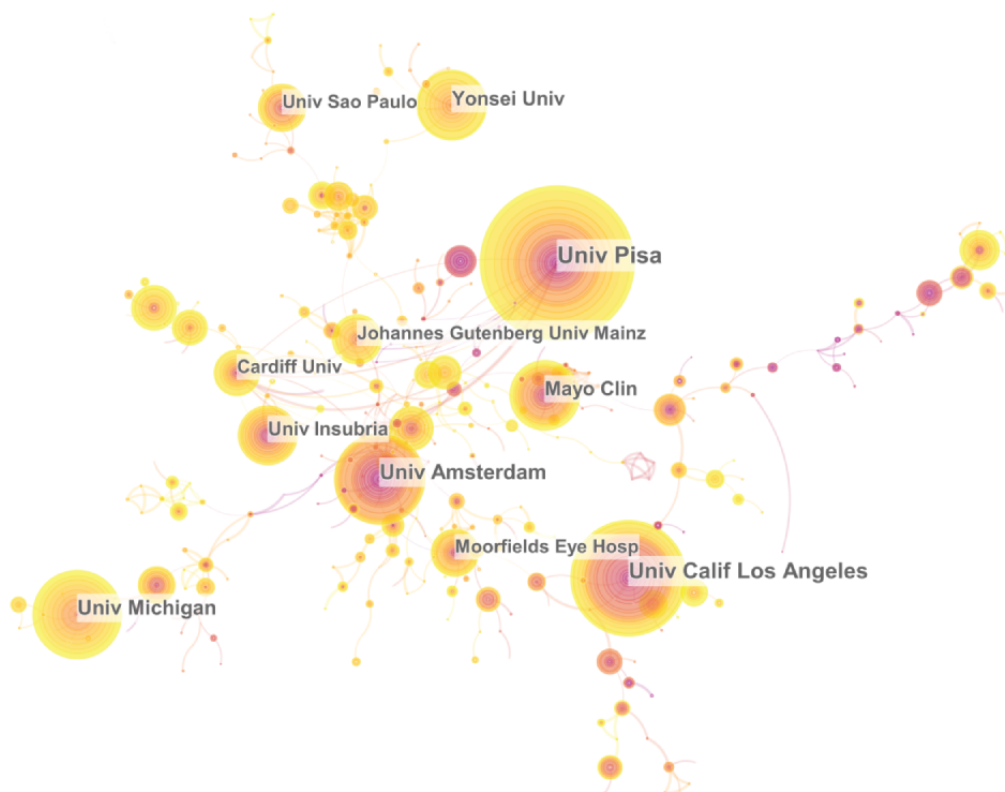
Figure 5. Institution co-operation network.

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Table 4. Top 10 institutions publishing the most articles.

Rank	Institution	Publications, n	Percentage of 3051	Country
1	University of Pisa	114	3.7	Italy
2	University of California, Los Angeles	91	3.0	United States
3	Universiteit van Amsterdam	72	2.4	Netherlands
4	University of Michigan	69	2.3	United States
5	Mayo Clinic	59	1.9	United States
6	Yonsei University	52	1.7	South Korea
7	University of Insubria	50	1.6	Italy
8	Johannes Gutenberg University Mainz	46	1.5	Germany
9	University of Sao Paulo	45	1.5	Brazil
10	Moorfields Eye Hospital	43	1.4	United Kingdom

Analysis of Keywords

Keyword analysis using CiteSpace revealed a network of keywords, where larger nodes indicated a higher occurrence. As shown in Figure 6, *Graves ophthalmopathy* occurred most frequently (n=815), followed by *ophthalmopathy* (n=751) and *Graves disease* (n=706). Next, keywords were sorted by burst strength; the top 30 keywords with the strongest citation bursts are presented in Figure 7. The occurrence of a burst indicates a sharp increase in keyword occurrence during a specific period and represents hot topics and field dynamics. The analysis of keyword bursts continuing until 2019 could indicate hot topics in the field of Graves ophthalmopathy research. Of the 30 bursts detected, proliferation (2013–2019), rituximab (2014-2019), and selenium (2015-2019) were hot topics in recent years. *Graves orbitopathy* was also a burst keyword; however, it is a theme word and cannot be considered a hot topic.
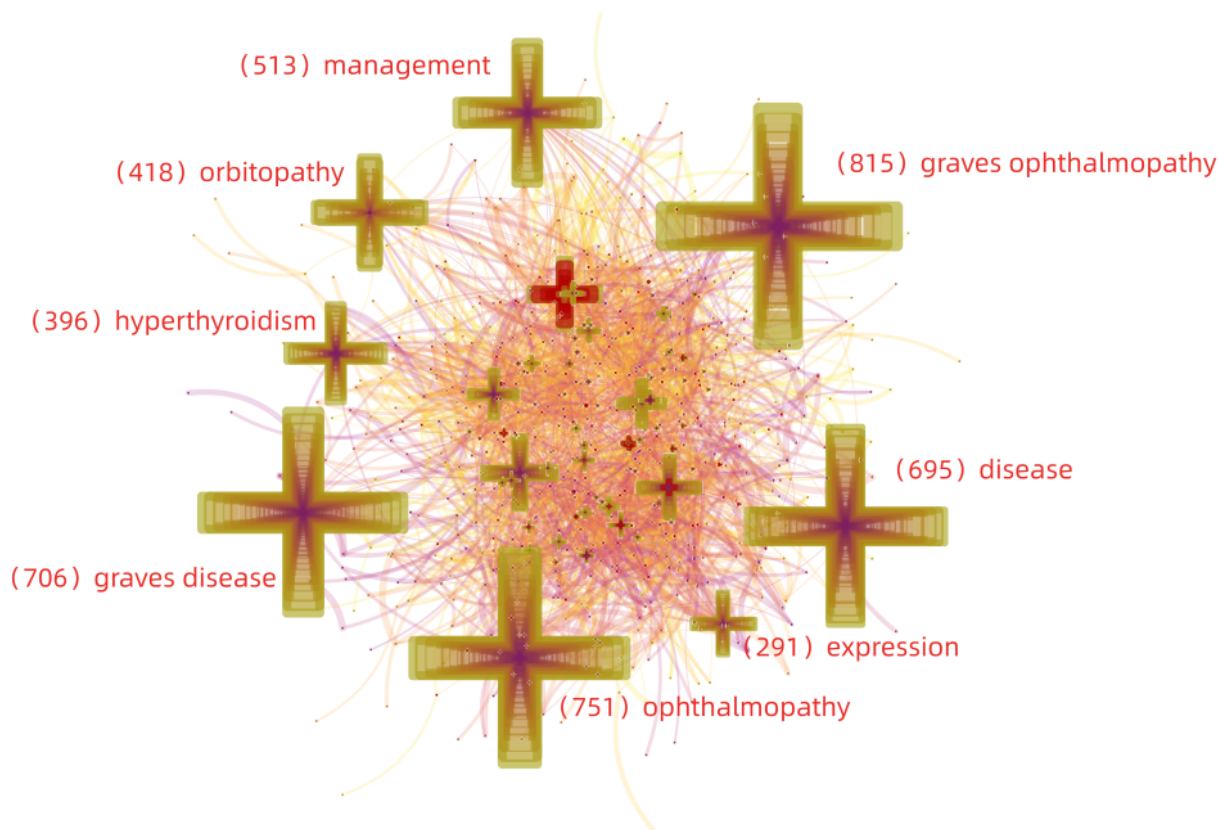
Figure 6. Keywords network.

Figure 7. Top 30 strongest burst keywords.

Keywords	Year	Strength	Begin	End	1999 - 2019
connective tissue	1999	12.7935	1999	2005	
endocrine ophthalmopathy	1999	11.2823	1999	2008	
thyrotoxicosis	1999	9.3385	1999	2005	
endoperoxide h synthase 2	1999	7.3648	1999	2008	
tissue	1999	7.3365	1999	2004	
messenger rna	1999	7.2576	1999	2004	
radiotherapy	1999	6.4866	1999	2003	
localization	1999	6.1308	1999	2001	
interferon gamma	1999	6.125	1999	2006	
human thyrotropin receptor	1999	5.9207	1999	2002	
leukoregulin induction	1999	5.7009	1999	2004	
eye disease	1999	6.2499	2000	2001	
human orbital fibroblast	1999	5.5209	2000	2010	
cigarette smoking	1999	8.33	2001	2006	
corticosteroid	1999	6.523	2001	2004	
thyrotropin receptor	1999	5.462	2002	2005	
go qol	1999	5.7531	2004	2011	
hyaluronan synthesis	1999	6.3092	2005	2010	
autoimmune thyroid disease	1999	5.4487	2005	2009	
rheumatoid arthriti	1999	7.7687	2006	2010	
factor i receptor	1999	10.177	2008	2013	
monoclonal antibody rituximab	1999	8.1097	2008	2011	
modulation	1999	5.5525	2011	2013	
thyroid-associated	1999	6.6863	2013	2016	
proliferation	1999	6.1714	2013	2019	
complication	1999	5.6403	2013	2017	
natural history	1999	9.8989	2014	2016	
rituximab	1999	7.068	2014	2019	
graves orbitopathy	1999	21.7637	2015	2019	
selenium	1999	7.192	2015	2019	

Analysis of References

Reference analysis is an important part of the bibliometric studies. Reference analysis using CiteSpace generated a reference network, illustrating the relationships among the reference citations. The top 30 strongest reference bursts, which can be considered fundamental knowledge in the field, are presented in Figure 8. Bahn RS (2010) [21] led the citation bursts to 2019, followed by Bartalena et al [4] and Smith et al [1] (Figure 9).
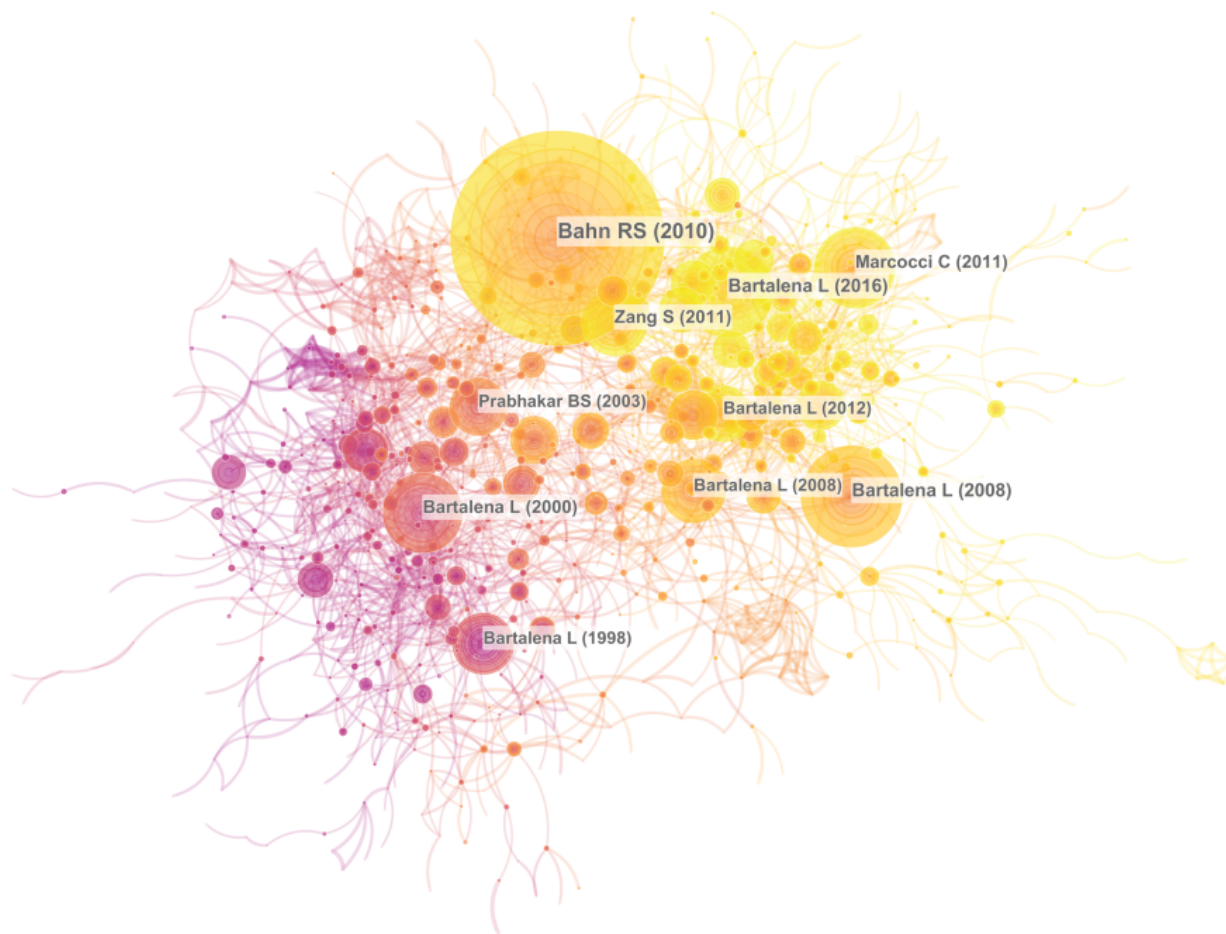
Figure 8. Reference network.

Figure 9. Top 30 strongest references.

References	Year	Strength	Begin	End	1999 - 2019
Bartalena L, 1998, NEW ENGL J MED, V338, P73, DOI	1998	41.7055	1999	2006	
BURCH HB, 1993, ENDOCR REV, V14, P747, DOI	1993	32.6866	1999	2001	
Bahn RS, 1998, J CLIN ENDOCR METAB, V83, P998, DOI	1998	32.6364	1999	2006	
BAHN RS, 1993, NEW ENGL J MED, V329, P1468	1993	31.5127	1999	2001	
Mourits MP, 1997, CLIN ENDOCRINOL, V47, P9, DOI	1997	21.5485	1999	2005	
Bartalena L, 2000, ENDOCR REV, V21, P168, DOI	2000	55.7942	2001	2008	
Weetman AP, 2000, NEW ENGL J MED, V343, P1236, DOI	2000	27.2816	2001	2008	
Gerding MN, 2000, CLIN ENDOCRINOL, V52, P267, DOI	2000	23.4235	2001	2008	
Gorman CA, 2001, OPHTHALMOLOGY, V108, P1523, DOI	2001	20.0357	2002	2009	
Wakelkamp IMMJ, 2003, CLIN ENDOCRINOL, V58, P280, DOI	2003	21.5169	2003	2011	
Bahn RS, 2003, J CLIN ENDOCR METAB, V88, P1939, DOI	2003	26.2674	2004	2011	
Prabhakar BS, 2003, ENDOCR REV, V24, P802, DOI	2003	41.4749	2005	2011	
Eckstein AK, 2006, J CLIN ENDOCR METAB, V91, P3464, DOI	2006	28.346	2007	2014	
Smith TJ, 2004, J CLIN ENDOCR METAB, V89, P5076, DOI	2004	20.1847	2007	2012	
Salvi M, 2007, EUR J ENDOCRINOL, V156, P33, DOI	2007	19.5339	2007	2014	
Bartalena L, 2008, EUR J ENDOCRINOL, V158, P273, DOI	2008	44.1129	2009	2016	
Bartalena L, 2008, THYROID, V18, P333, DOI	2008	29.1602	2009	2016	
Wiersinga WM, 2006, EUR J ENDOCRINOL, V155, P387, DOI	2006	19.0598	2009	2014	
Bartalena L, 2009, NEW ENGL J MED, V360, P994, DOI	2009	22.7543	2010	2016	
Bahn RS, 2010, NEW ENGL J MED, V362, P726, DOI	2010	67.0398	2011	2019	
Marcocci C, 2011, NEW ENGL J MED, V364, P1920, DOI	2011	24.4291	2012	2019	
Bartalena L, 2012, J CLIN ENDOCR METAB, V97, P4454, DOI	2012	21.1933	2013	2019	
Tanda ML, 2013, J CLIN ENDOCR METAB, V98, P1443, DOI	2013	21.3302	2014	2019	
Zang S, 2011, J CLIN ENDOCR METAB, V96, P320, DOI	2011	20.2002	2014	2019	
Stan MN, 2015, J CLIN ENDOCR METAB, V100, P432, DOI	2015	23.7767	2015	2019	
Bartalena L, 2014, J ENDOCRINOL INVEST, V37, P691, DOI	2014	20.4969	2015	2019	
Wang Y, 2014, INVEST OPHTH VIS SCI, V55, P1735, DOI	2014	19.8442	2015	2019	
Salvi M, 2015, J CLIN ENDOCR METAB, V100, P422, DOI	2015	25.742	2016	2019	
Bartalena L, 2016, EUR THYROID J, V5, P9, DOI	2016	63.5637	2017	2019	
Smith TJ, 2016, NEW ENGL J MED, V375, P1552, DOI	2016	29.1747	2017	2019	

Discussion

Principal Findings

In this study, a bibliometric analysis of Graves ophthalmopathy publications from 1999 to 2019 was conducted using CiteSpace, GraphPad Prism 8, SPSS, and web-based bibliometric analysis platforms. Our exponential fitting curve analysis results show that the number of publications continues to increase, indicating that more research and articles will contribute to this field. Hence, the Graves ophthalmopathy field will continue to be a hot topic in the future, both because of the many points requiring clarification and the substantial physical and mental impacts of Graves ophthalmopathy on patients.

Of the top 10 profiled countries, 9 were high-income nations, with China being the only low-income country. The United States had the largest number of Graves ophthalmopathy research outputs (n=784) and the highest centrality (0.18). China had 350 Graves ophthalmopathy research outputs, ranking second in terms of the number of publications. As a transitional country, China has the potential to progress much further in Graves ophthalmopathy research and would benefit from more co-operation with other countries. The top 10 institutions were

responsible for a total of 641 publications (20% of 3051), and 8 were colleges and universities in high-income countries, including the United States (n=2), Italy (n=2), the Netherlands (n=1), South Korea (n=1), Germany (n=1), and 1 transitional country, Brazil (n=1). The other 2 institutions, the Mayo Clinic and Moorfields Eye Hospital, were hospitals in the United States and the United Kingdom, respectively. The number of publications may be related to economic prosperity at the country level.

Some excellent authors have been identified in our analysis. Smith TJ had the largest number of Graves ophthalmopathy–related publication outputs (n=83) over the last 20 years; Marcocci C (n=73) ranked second, and Kahaly GJ (n=68) ranked third. The H-index is used to describe the breadth of the impact of an author's scientific research. Wiersinga WM had the highest H-index (75), despite not having the most Graves ophthalmopathy–related publication outputs over the last 20 years. All these authors devoted themselves to the development of this field. For example, Smith TJ found that patients with Graves ophthalmopathy had higher levels of fibrocytes in the blood than those without Graves ophthalmopathy [22]. Furthermore, Marcocci et al [23] found

that patients with Graves ophthalmopathy who undergo total thyroid ablation may have better outcomes and health improvements than those who undergo thyroidectomy alone. Moreover, Kahaly et al [24] reported that teprotumumab resulted in better outcomes than treatment with a placebo.

As shown in Figure 7, burst keywords were detected using CiteSpace. Among the top 30 strongest burst keywords, proliferation, rituximab, and selenium remained burst keywords by the end of 2019, suggesting that they may occur frequently in the coming years and represent emerging trends. These burst keywords were introduced as follows.

Proliferation

As Graves ophthalmopathy is an autoimmune disease, inflammation of orbital tissue is commonly involved, according to recent research. The proliferation of fibrocytes and fibroblasts is considered an important aspect of the pathogenesis of Graves ophthalmopathy. Many studies have focused on the regulation of fibroblast proliferation, with the aim of determining possible Graves ophthalmopathy therapy approaches. For example, gypenosides promote fibroblast proliferation, inflammation, and fibrosis to regulate Graves ophthalmopathy progression [25]. Furthermore, chitosan inhibits fibroblast proliferation and adipogenesis, which may have therapeutic effects on Graves ophthalmopathy [26]. Although there are many other biological processes, including cell death and degeneration, the inclusion of proliferation as a burst keyword may predict that more research in this field will focus on this cellular process in the future.

Selenium

Selenium was identified as a component of an enzyme that activates thyroid hormones in the 1990s. Selenium supplementation can regulate thyroid function by decreasing serum T4 concentration, and pregnant women with GD have lower selenium levels than those without GD [27]. Research on the effects of selenium on Graves ophthalmopathy suggests that it may improve disease outcomes by preventing cell damage and decreasing cytotoxic oxidative stress damage to fibroblasts [28]. Indeed, there are many adjuvant therapies available, among which supplementation with selenium is a major method recommended in the 2016 European Thyroid Association/European Group on Graves Orbitopathy Guidelines for improvement of eye function and quality of life [4]; however, the mechanism by which selenium improves the manifestations of Graves ophthalmopathy remains unclear. Therefore, research into selenium may be a future trend.

Rituximab

There has been substantial research into the effects of rituximab in Graves ophthalmopathy therapy, and many clinical trials have demonstrated that rituximab has therapeutic effects, with limited side effects [29]. As an anti-CD20 monoclonal antibody, rituximab can inhibit B cell activation and decrease inflammatory cytokine secretion [29]. As modern therapy strategies for Graves ophthalmopathy are concerned with individualization and precision, immune-based therapies have become increasingly popular, and numerous antibodies have been applied as new therapies. As one such antibody therapy

method, rituximab has been researched in randomized controlled trials and fundamental research [29-32]. Additional research into this burst keyword will provide more detailed data in the coming years.

Research frontiers can be explored by identifying the most recent burst citations. As shown in Figure 9, the top five burst citations with the highest strength at the end of 2019 were as follows: (1) Bahn et al [21], which reviewed Graves ophthalmopathy knowledge and described the clinical and laboratory features of Graves ophthalmopathy, as well as its pathogenesis and therapeutic approaches; (2) Bartalena et al [4] listed current therapeutic recommendations for patients with different degrees of Graves ophthalmopathy; (3) Smith et al [1] described the clinical manifestations, pathogenesis, diagnosis, and therapy of GD, where Graves ophthalmopathy was considered an extrathyroid complication, the pathogenesis and manifestations of which are established; (4) Salvi et al [32] reported a randomized controlled trial on the effects of rituximab as therapy for active moderate to severe Graves ophthalmopathy, which demonstrated that rituximab led to better outcomes than intravenous methylprednisolone; and (5) Marcocci et al [33] demonstrated that selenium significantly improved outcomes in patients with Graves ophthalmopathy, compared with placebo in a randomized controlled trial, illustrating the importance of selenium supplementation for patients with Graves ophthalmopathy.

With the increasing amount of literature, visualization of data has become increasingly important and difficult for researchers to understand the current research progress from a large perspective [8]. As a tool software, CiteSpace explores future development trends and grasps the knowledge network map of Graves ophthalmopathy as a whole, rather than just aiming at a special topic such as typical reviews [13]. This study provides a reference for other researchers to understand the current research status and possible future directions in the field of Graves ophthalmopathy. The trend of further increase in the number of studies would attract more attention from researchers and further promote the development of this field. The analysis of references pointed out useful classical literature that could be regarded as the research cornerstone in this field and may help researchers understand the field of Graves ophthalmopathy faster and better. The analysis of the burst keyword indicated a possible future development direction in this field. Proliferation, selenium, and rituximab may represent the development direction of the mechanism and treatment in the field of Graves ophthalmopathy, respectively. Co-operation among authors, institutions, and countries would provide a reference for the introduction of academic resources, the development of co-operation, and the evaluation of academic achievements [13]. In addition, bibliometric and visual analysis and the use of CiteSpace were not only limited to the research in the field of Graves ophthalmopathy but also could be used in other fields because every discipline has its unique knowledge network system.

To our knowledge, this is the first bibliometric analysis of Graves ophthalmopathy using publication outputs from the Web of Science from 1999 to 2019. This study has some limitations. Although we attempted to collect all reports on Graves

ophthalmopathy over the last 20 years, some were not included, such as gray literature and related reports in databases other than WoSCC. Furthermore, some recent articles will likely accrue more citations in the future, which may have led to the exclusion of high-quality studies from this analysis. Moreover, the number of citations does not fully represent the importance of an article, as some important articles may have few citations and self-citations can cause bias.

In conclusion, this bibliometric analysis highlights possible emerging trends in Graves ophthalmopathy research through analysis of publication outputs from 1999 to 2019, as well as the contributions of countries, institutions, authors, and journals. These results may inform clinical decision-making and future research.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Researching strategies and results.
[RAR File , 4678 KB - ijmr_v10i3e24831_app1.rar]

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Abbreviations

GD: Graves disease
H-index: Hirsch index
IF: impact factor
WoSCC: Web of Science Core Collection Database

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