Good’s syndrome (GS) is a rare disease characterized by thymoma, hypogammaglobulinemia, decreased T-cells, an inverted CD4+/CD8+ T-cell ratio and reduced T-cell mitogen proliferative responses. GS is difficult to diagnose preoperatively due to its rarity and lack of typical symptoms, the characteristics of Chinese GS patients are still lacking. This study aimed to systematically review all the clinical, laboratory, and immunologic findings of reported cases of Chinese patients with GS.

Methods: We searched for case reports and articles up to January 2017 using PubMed, China National Knowledge Infrastructure, Wangfang database and China Science and Technology Journal Database with the following words in combinations as key words: “thymoma,” “hypogammaglobulinemia,” and “Good’s syndrome.” The text words and MeSH terms were entered depending on the databases characteristics. The reference lists from retrieved articles were also screened for additional applicable studies. The authors were restricted to Chinese. There was no language restriction.

Results: Forty-seven patients were reported in 27 studies. We found that GS has a nationwide distribution and that most cases (83%) have been described on the mainland of China. The initial clinical presentation is varied, ranging from symptoms related to the thymoma to infections resulting from immunodeficiency. Type AB (50%) is the most common histologic type of thymomas in Chinese GS patients according to the World Health Organization classification of thymomas. With respect to infection, sinopulmonary infection (74%) is the most common type, followed by skin infection (10%) and intestinal tract infection (10%). Diarrhea was presented in 36% of patients, and autoimmune manifestations were presented in 36% of patients.

Conclusions: GS is a rare association of thymoma and immunodeficiency with a poor prognosis. Astute clinical acumen and increased awareness of the clinical and immunological profile of GS are needed to increase early diagnosis, that would benefit improved therapeutic effects.

Key words: Agammaglobulinemia; Diarrhea; Good’s Syndrome; Immunologic Deficiency Syndromes; Thymoma
Methods

Search strategy
We searched for all cases and articles up to January 2017 using the PubMed, China National Knowledge Infrastructure database, Wangfang database and China Science and Technology Journal Database with the following words in combinations as key words: “thymoma,” “hypogammaglobulinemia,” and “Good’s syndrome.” The text words and MeSH terms were entered depending on the databases characteristics. The reference lists from retrieved articles were also screened for additional applicable studies. We considered completed published studies as well as abstracts presented at meetings. Authors of relevant studies were contacted regarding unpublished cases. The authors were restricted to Chinese. There was no language restriction. The flowchart of the review search and identification is shown in Figure 1.

Inclusion and exclusion criteria
Since there were a number of definitions for GS, we defined GS as a constellation of thymoma and adult-onset immunodeficiency characterized by hypogammaglobulinemia, low or absent B-cells, variable defects in cell-mediated immunity with a CD4+ T lymphopenia, an inverted CD4+/CD8+ T-cell ratio and reduced T-cell mitogen proliferative responses according to Kelesidis and Yang definition. We included cases and observational studies that reported GS, regardless of publication status.

Study selection
Two authors independently scanned the titles, authors, and abstracts of the reports to identify eligible articles. We attempted to locate the full text if we could not judge whether an article was in keeping with the inclusion and exclusion criteria. Any disagreement was resolved by discussion; a third reviewer was consulted if we could not reach a consensus.

Results

Study identification
Thirty studies were identified after screening the titles, abstracts, and authors, four of which were excluded (two did not qualify as diagnoses of GS whereas the other two were excluded because they reported the same patients as other studies). An unpublished case report of GS was also included. Finally, 47 patients were reported in 27 studies. Thirty-nine (83%, 39/47) patients were reported in the mainland of China, five (11%, 5/47) in Taiwan (China), three (6%, 3/47) in Hong Kong (China). Sixteen (59%, 16/27) studies were published in Chinese, and 11 were published in English.

Figure 1: Flowchart of the review search and identification.
Gastrointestinal manifestations
Diarrhea was present in 36% (17/47) of patients. Infection is one of the causes, but not the main cause.

Autoimmune manifestations
Seventeen patients (36%, 17/47) presented autoimmune manifestations. We summarized the autoimmune manifestations of the 17 patients in Table 3.

Laboratory data
The laboratory findings in patients with GS were presented in Table 4.

Other manifestations
Hearing loss was presented in four patients, one of them due to frequentative auditory tube infection, the other three without definitive cause.

Discussion
GS was classified as a distinct entity involving primary immunodeficiencies in 1999 by the expert committee of the WHO and International Union of Immunological Societies.[34] Its peak incidence is between the ages of 40 and 50 years.[35] Foreign literatures report males and females are equally affected, but we found females are more inclined to suffer GS in Chinese patients. GS can also occur in children, although this is extremely rare.[36]

The pathogenesis of GS remains unknown. There are two possible mechanisms for the association between hypogammaglobulinemia and thymoma. The first is that cytokines secreted by bone marrow stromal cells might influence the growth and differentiation of both thymic and B‑cell precursors. The second is that T‑cells isolated from patients with thymoma might inhibit pre‑B‑cell growth and immunoglobulin production by B‑cells. However, neither hypothesis is widely accepted.

The diagnosis of thymoma might occur preceding, after or simultaneously with other clinical manifestations. Patients might complain of symptoms that are secondary

### Table 1: Histologic type of thymomas in Chinese patients with GS according to the WHO classification (n = 28)

| Histologic type of thymoma | Number of cases, n (%) |
|----------------------------|------------------------|
| Type AB                    | 14 (50)                |
| Type A                     | 10 (36)                |
| Type B2                    | 2 (7)                  |
| Type B3                    | 1 (4)                  |
| Malignant thymoma          | 1 (4)                  |

GS: Good’s syndrome; WHO: World Health Organization.

### Table 2: Infections described in 42 Chinese patients with GS

| Infection                  | Number of patients* | Pathogens                                  | Number of patients |
|----------------------------|---------------------|--------------------------------------------|--------------------|
| Sinopulmonary infection    | 31                  | CMV                                        | 7                  |
| Skin infection             | 4                   | Pseudomonas aeruginosa                     | 5                  |
| Intestinal tract infection | 4                   | Pneumocystis carinii pneumonia             | 4                  |
| Eye infection              | 2                   | Klebsiella pneumoniae                      | 3                  |
| Encephalitis               | 2                   | Herpes zoster                              | 3                  |
| Urinary tract infection    | 1                   | Staphylococcus aureus                      | 2                  |
| Spontaneous peritonitis    | 1                   | Clostridium difficile                      | 2                  |
| Joint infection            | 1                   | Herpes simplex                             | 1                  |
| Intra-abdominal infection  | 1                   | Mucor                                      | 1                  |
| Carbuncle                  | 1                   | Tuberculosis                               | 1                  |
| Cellulitis                 | 1                   | Toxoplasma gondii                          | 1                  |
| Viremia                    | 1                   | Staphylococcus                             | 1                  |
|                            |                     | Escherichia coli                           | 1                  |
|                            |                     | Haemophilus influenzae                     | 1                  |

*Some patients suffered more than one site infection. CMV: Cytomegalovirus; GS: Good’s syndrome.
to the thymoma. Superior vena cava syndrome, Horner’s syndrome, and masses in the neck have also been reported as initial manifestations. The most common histologic types of thymoma in GS is the AB variant (WHO classification),[1] which is in accordance with our study. Thymoma can be diagnosed by posteroanterior chest X-ray, which has a detection rate of 80%. Because the features of thymoma on chest X-rays may be subtle, in one study, 25% of tumors were missed, with a diagnostic delay of 41 months.[38] Therefore, a CT scan of the chest is recommended when a clinician is highly suspicious of thymoma, even the X-ray is negative. As the association between thymoma and immunodeficiency is not generally well known, it may be advisable to measure quantitative immunoglobulin levels in all patients with thymoma to diagnose and treat at an early stage the 3–6% who have or will develop GS.[19,40] In this study, we found the diagnosis of thymoma followed the emergence of other symptoms in more than half of patients. Therefore, we suggest doctors conduct relevant examinations to detect thymoma in patients with hypogammaglobulinemia and decreased peripheral blood lymphocytes.

Due to both humoral and cell-mediated immune deficiencies, GS patients can easily contract various infections, including bacterial, fungal, viral, and other opportunistic infections. For bacterial infections, recurrent infections of the upper and lower respiratory tract are the most common,[1,38] with common pathogens including *Haemophilus influenzae*, *Pseudomonas* spp., and *Klebsiella* spp.[1] Bronchiectasis might also develop in GS patients. Among fungal infections, Kelesidis and Yang reported *Candida* is the most common pathogen,[1] but we found *Pneumocystis jirovecii* is more common. Among viral infections, myasthenia gravis (MG) and GS is unknown, doctors could pay attention to this aspect to confirm it in the future.

A variety of autoimmune manifestations might present in GS patients, the most common of which is PRCA, followed by myasthenia gravis. A systematic review suggested that autoantibodies can be detected in more than half (56%) of patients with GS, and autoantibodies (ANAs) are the most common autoimmune antibodies, accounting for 55%.[1] However, we found only 1/8 patient with ANA positive. This is an interesting phenomenon, considering a bias may be introduced due to a small sample size in our study, we need more studies to confirm whether there is a difference between Chinese and Western in autoantibodies.

Four patients presented hearing loss, this is beyond previous literature reports. One of them was due to frequentative auditory tube infection, the other three without definitive cause. Whether there is a relationship between hearing loss and GS is unknown, doctors could pay attention to this aspect to confirm it in the future.

Thus far, GS has no definitive therapeutic schedule, but thymectomy and immunoglobulin replacement treatment have become the most important management approach. Thymectomy has a positive effect on myasthenia gravis and PRCA, although it has no effect on immunological
In one case, thymectomy might have worsened the hypogammaglobulinemia. Immunoglobulin replacement treatment has been reported to play a favorable role in controlling infection. A retrospective report highlighted that 23 of 30 patients had a reduction of bacterial sinopulmonary infections after receiving immunoglobulin treatment. Intravenous immunoglobulin (IVIG) was superior to intramuscular immunoglobulin replacement (response rate of 88% vs. 62%).

Common variable immune deficiency (CVID) is one of the most common symptomatic primary immunodeficiency syndromes in China, which is also characterized by hypogammaglobulinemia and recurrent infections. However, in contrast to CVID, which typically occurs in the pediatric population, GS has a poorer prognosis with a high mortality of approximately 45–57%, with infection being the most common cause of death. In a single-center review of primary antibody deficiency spanning 20 years, 70% of patients with GS were alive 5 years after the onset of symptoms, compared with almost 100% of patients with CVID. At 10 years, only 33% were alive, compared with 95% of patients with CVID. Other causes contributing to death are an autoimmune disease and hematological complications. The prognosis is mainly determined by the severity of associated infectious, hematologic, and autoimmune diseases, rather than by the behavior of the thymoma.

There are some limitations to this systematic review. First, the amount of included studies is small. Second, the studies included were case reports or case studies, which might decrease the quality of evidence, more studies of high quality are required to unravel the mystery of GS.

In conclusion, GS is a rare association of thymoma and immunodeficiency with a poor prognosis. The initial clinical presentation is varied, ranging from symptoms related to the thymoma to infections resulting from immunodeficiency. Gastrointestinal and autoimmune manifestations are common complications. With respect to treatment, thymectomy and IVIG are the primary GS therapies. Astute clinical acumen and increased awareness regarding the clinical and immunological profile of this syndrome might increase the early recognition of this syndrome and decrease the mortality.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Kelesidis T, Yang O. Good’s syndrome remains a mystery after 55 years: A systematic review of the scientific evidence. Clin Immunol 2010;135:347-63. doi: 10.1016/j.clim.2010.01.006.
2. Good RA. Agammaglobulinemia: A provocative experiment of nature. Bull Univ Minn Hosp 1954;26:1-19.
3. Zhang Y, Han YQ. Care of a patient with Good’s syndrome and red man syndrome, a case report (in Chinese). Chin Nurs Res 2011;25:1406-7. doi: 10.3969/j.issn.1009-6493.2011.15.059.
4. Peng JM, Sun G, Xu DB. A case report of Good’s syndrome (in Chinese). Chin J Pract Intern Med 2004;24:256. doi: 10.3969/j.issn.1005-2194.2004.04.031.
5. Guo Z, Zhang SF. A case report of Good’s syndrome. Prac J Med and Pharm 2011;28:550. doi: 10.14172/cjki.issn1671-4008.2011.06.058.
6. Huang H, Song CY, Lai XH, Chen D, Li GM, Shi LW. A case report of Good’s syndrome with pulmonary mucormycosis (in Chinese). Chin J Diffic Compl Cases 2010;9:149-50. doi: 10.3969/j.issn.1671-6450.2010.02.039.
7. Wang J, Feng GD, Yang YN, Wu ZL, Zhao G. A case report of Good’s syndrome with chronic herpes simplex encephalitis (in Chinese). Chin J Diffic Compl Cas 2013;12:471. doi: 10.3969/j.issn.1671-6450.2013.06.025.
8. Sun Y. A case report of Good’s syndrome with refractory fever (in Chinese). Tianjin Med J 2012;40:1267-8. doi: 10.3969/j.issn.0253-9896.2012.12.032.
9. Zhao TM, Xie LX, Wang YP, Wang QX, Qi F, Chen LA. A case report of Good’s syndrome with repeated respiratory tract infection and failure and literature review (in Chinese). Beijing Med J 2008;50:177-8. doi: 10.15932/j.0253-9713.2008.03.025.
10. Liu EW, Xie MJ, Ge LA. Traditional Chinese medicine treat refractory diarrhea induced by long-term use of antibiotics in a Good’s syndrome patient: A case report (in Chinese). Jiangxi J Tradit Chin Med 2013;44:43-4. doi: 10.3969/j.issn.0411-9497.2012.11.005.
11. Li XY, Zhuang SX. A case report of Good’s syndrome with leukopenia (in Chinese). Chin J Hematol 2010;31:544. doi: 10.3969/j.issn.0253-2727.2010.08.011.
12. Li YS, Jiang Y, Zuo XX. A case report of Good’s syndrome with joint infection (in Chinese). Chin J Intern Med 2011;50:964-5. doi: 10.3760/cma.j.issn.0578-1426.2011.11.017.
13. Zeng H, Liao LY, Lv HN. A case report of Good’s syndrome with original diarrhea symptom and literature review (in Chinese). Chin J Dig 2008;28:352-4. doi: 10.3760/j.issn.0254-1432.2008.05.024.
14. Wang YX, Tian XP, Zhang Y, Zhao Y, Dong Y. Clinical analysis of 10 Good’s symptom cases (in Chinese). Natl Med J Chin 2011;91:1490-2. doi: 10.3760/cma.j.issn.0376-2491.2011.21.014.
15. Yong DS, Tsang MK, Chan EY, Tse DM. Good’s syndrome in a patient with *Cytomegalovirus* infection. Hong Kong Med J 2008;14:142-4.
16. Wong IW, Chan KK, Chan KS. Good’s syndrome. Hong Kong Med J 2008;14:246.
17. Wang CH, Chan ED, Perng CL, Chian CF, Chen CW, Perng WC, et al. Intravenous immunoglobulin replacement therapy to prevent pulmonary infection in a patient with Good’s syndrome. J Microbiol Immunol Infect 2015;48:229-32. doi: 10.1016/j.jmii.2012.09.003.
18. Liu SC, Wang CH. Multiple head and neck tuberculosis granulomas in a patient with thymoma and immunodeficiency (Good’s syndrome). Otolaryngol Head Neck Surg 2010;142:454-5. doi: 10.1016/j.otohns.2009.10.034.
19. Chen LP, Tsai JS, Lai WM, Yen LJ, Yu MS, Lin SJ. Myelodysplasia followed by Good’s syndrome: A unique manifestation associated with thymoma. Kaohsiung J Med Sci 2012;28:236-40. doi: 10.1016/j.kjms.2011.01.012.
20. Lin CS, Yu YB, Hsu HS, Chou TY, Hsu WH, Huang BS. Pure red cell aplasia and hypogammaglobulinemia in a patient with thymoma (in Chinese). J Chin Med Assoc 2009;72:34. doi: 10.1016/S1726-4901(09)70017-6.
21. Tsai YG, Lai HK, Kuo SY, Chen HC, Chang DM. Thymoma and hypogammaglobulinemia (Good’s syndrome): A case report. J Microbiol Immunol Infect 2005;38:218-20.
22. Hon C, Chui WH, Cheng LC, Shek TW, Jones BM, Au WY. Thymoma associated with keratoconjunctivitis, lichen planus, hypogammaglobulinemia, and absent circulating B cells. J Clin Oncol 2006;24:2960-1. doi: 10.1200/jco.2005.04.3133.
23. Chen J, Yang Y, Zhu D, Chen G, Wei S, Qiu X, et al. Thymoma with pure red cell aplasia and Good’s syndrome. Ann Thorac Surg 2011;91:1620-2. doi: 10.1016/j.athoracsur.2010.10.010.
24. Li R, Ma YL, Wei JA, Han F, Cao ZL, Gao ZC. Three case reports
of Good’s syndrome with pulmonary lesions and literature review (in Chinese). Chin J Gen Pract 2014;13:308-10. doi: 10.3760/cma.j.issn.1671-7368.2014.04.022.

26. Tian WW, Liu DP, Biao SC, Ma LM, Wang T, Xie YX, et al. Polycythemia vera with Good’s syndrome and agranulocytosis: Report of a case and literatures review (in Chinese). Chin J Hematol 2016;37:522-4. doi: 10.3760/cma.j.issn.1671-6821.2016.05.034.

27. Xi XY, Wang M, Zhou SF, Wu WY. Malabsorption syndrome as the main symptom: A case report of Good’s syndrome with malabsorption syndrome and literatures review (in Chinese). Chin J Intern Med 2016;55:800-2. doi: 10.3760/cma.j.issn.0578-1426.2016.10.017.

28. Xu L, Ma GF, Ying KJ. A case report of Good’s syndrome (in Chinese). China Clin Pract Med 2016;7:97-7. doi: 10.3760/cma.j.issn.1673-8799.2016.05.035.

29. Sun X, Shi J, Wang M, Xu K, Xiao Y. Good’s syndrome patients hospitalized for infections: A single-center retrospective study. Medicine (Baltimore) 2015;94:e2090. doi: 10.1097/md.0000000000002090.

30. Dong JP, Gao W, Teng GG, Wang HH. A case report of Good’s syndrome. [Unpublished Observations].

31. Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. International Union of Immunological Societies. Clin Exp Immunol 1999;118 Suppl 1:1-28. doi: 10.1046/j.1365-2249.1999.00109.x.

32. Good RA, Maclean LD, Varco RL, Zak SJ. Thymic tumor and acquired agammaglobulinemia: A clinical and experimental study of the immune response. Surgery 1956;40:1010-7.

33. Watts RG, Kelly DR. Fatal varicella infection in a child associated with thymoma and hypogammaglobulinemia (Good’s syndrome). South Med J 1997;90:444-6.

34. Hughes WS, Cerda JJ, Holtzapple P, Brooks FP. Primary hypogammaglobulinemia and malabsorption. Ann Intern Med 1971;74:903-10. doi: 10.7326/0003-4819;74-6-903.

35. Ohuchi M, Inoue S, Hanaoka J, Igarashi T, Tezuka N, Ozaki Y, et al. Good syndrome coexisting with leukopenia. Ann Thorac Surg 2007;84:2095-7. doi: 10.1016/j.athoracsur.2007.06.070.

36. Lin LJ, Wang YC, Liu XM. Clinical and immunological features of common variable immunodeficiency in China. Chin Med J 2015;128:310-5. doi: 10.4103/0366-6999.150092.

37. Veen MH, Palalay MP, Sonido CY. Case report and literature review on Good’s syndrome, a form of acquired immunodeficiency associated with thymomas. Hawaii J Med Public Health 2013;72:56-62.

38. Gray GF, Gutsowki WT 3rd. Thymoma. A clinicopathologic study of 54 cases. Am J Surg Pathol 1979;3:235-49.