Unveiling Hidden Dangers: A Comprehensive Study of Thyroid Nodules and Malignancy Rates in the Galilee

Avichai Turjeman BScMed[1] and Ohad Ronen MD[1,2]

[1]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel
[2]Department of Otolaryngology–Head and Neck Surgery, Galilee Medical Center, Nahariya, Israel

ABSTRACT **Background:** Increased utilization of imaging modalities has led to a significant rise in the detection of incidental thyroid nodules (ITN). Discrepancies in the prevalence of thyroid nodules with malignant potential exist worldwide.

Objectives: To analyze demographic and clinical data among patients with thyroid nodules in our geographic region.

Methods: The medical records of patients diagnosed with symptomatic or incidental thyroid nodules at the Galilee Medical Center between 2018 and 2023 were reviewed. Demographic and clinical data were collected and analyzed.

Results: The study population included 402 patients with thyroid nodules, 292 females. Symptomatic patients were younger (mean age 55.9 vs. 60.8 years) and had larger nodules (mean size 2.5 vs. 2.1 cm) compared to incidentally diagnosed patients ($P < 0.001$, $P < 0.001$, respectively). Male patients demonstrated a higher rate of malignancy for both symptomatic and incidental nodules compared to females ($P < 0.05$). Pathological examination revealed that malignant nodules were smaller (mean size 2.10 cm vs. 2.87 cm) and detected at a younger age (mean age 48.56 years vs. 56.5 years), compared to benign nodules ($P < 0.05$, $P < 0.01$, respectively).

Conclusions: We found a higher prevalence of both symptomatic and ITN among females. However, malignant thyroid nodules were more frequently observed in males. Notably, malignant nodules tended to be smaller and were more commonly diagnosed in younger individuals compared to benign nodules. These findings highlight significant sex and age disparities in the occurrence and characteristics of thyroid nodules, emphasizing the need for tailored diagnostic and management strategies.

IMAJ 2025; 27: 642–647

KEY WORDS: Bethesda classification system, incidental thyroid nodule, malignancy, Thyroid Imaging Reporting and Data System (TIRADS), thyroid nodule

Thyroid nodules are common, with a prevalence of almost 25% in the general population. Their prevalence varies considerably depending on demographics such as age, sex, and the presence of risk factors [1]. Thyroid nodules can present as symptomatic findings or as an incidental identification during imaging performed for unrelated medical indications, referred to as incidental thyroid nodules, ITNs [1].

Studies have shown that 50–60% of patients undergoing imaging for non-thyroid-related conditions were found to have ITNs [1]. Today, ITNs are the most common incidental findings in imaging studies involving the neck [2].

The Thyroid Imaging Reporting and Data System (TI-RADS) classifies thyroid nodules based on malignancy risk, with scores ranging from 1 to 5 [3]. Fine needle aspiration (FNA) is the recommended diagnostic method, with results categorized by the Bethesda system, which assigns malignancy risk and management recommendations [4]. A meta-analysis published in 2021 reported malignancy rates for ITNs, ranging from 4% to 24% [1].

Considering the lack of clarity and frequency of thyroid nodules, we examined the clinical and demographic characteristics of thyroid nodules at a tertiary referral medical center, which serves a diverse population of 600,000 patients.

PATIENTS AND METHODS

In this retrospective data review, we examined records from the Department of Otolaryngology–Head and Neck Surgery and the Department of Pathology at Galilee Medical Center between 2018 and 2023.

STUDY POPULATION

The study population included patients of both sexes aged 18 years and older who were referred to our medical cen-

ter. The data collected focused on patients diagnosed with incidental or symptomatic thyroid nodules, incorporating demographic and clinical parameters, including sex, age, nodule size, and the classifications of the nodules according to TIRADS and Bethesda scoring systems.

STATISTICAL ANALYSIS

Quantitative data are presented as mean and standard deviations. Qualitative data, such as patient sex, are shown using frequency distributions, percentages, and graphical representations.

To compare qualitative data among the study groups, the chi-square test was used. For quantitative data analysis, the *t*-test was applied to normally distributed variables (e.g., age and Bethesda scores). In contrast, the Mann–Whitney U test was utilized for non-normally distributed variables (e.g., nodule size and TIRADS scores) for comparisons of ordinal variables within subgroups. A *P*-value < 0.05 (one-tailed) was considered statistically significant.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 28 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

The study population comprised of 402 patients with thyroid nodules. Of these, 292 were female (73%). The average age of male and female participants in the study was 59.5 and 58.6 years, respectively.

The classification of patients by sex and nodule type showed similar distributions between males and females [Figure 1]. Among female patients, 55% (n=160) had nodules discovered incidentally. Similarly, 57% (n=63) of male patients had ITNs, while 43% (n=47) were symptomatic.

The data presented in Table 1 show a statistically significant difference in the mean age of patients referred to as symptomatic or ITN. Symptomatic patients were younger (mean age 55.86 years vs. 60.82 years, $P < 0.001$). In addition, a significant difference in nodule size was observed. Symptomatic patients had a mean nodule size of 2.52 cm compared to 2.11 cm in the incidental group ($P < 0.001$). However, no statistically significant differences were found between the groups regarding TIRADS and Bethesda scores, with *P*-values of 0.458 and 0.091, respectively.

Table 2 highlights a significant difference between symptomatic and incidental patients. In symptomatic patients, ultrasound was the primary detection method in 97.2% (n=174) cases. In contrast, for incidental patients, computed tomography was the primary method in 62.3% (n=139) of cases (chi-square test, $P < 0.001$). When evaluating malignancy based on pathological results, no sig-

Table 1. Comparison between symptomatic and incidental patients regarding age, nodule size, TIRADS, and Bethesda scores

	Symptomatic patients	Incidental patients	*P*-value
	Mean ± SD	Mean ± SD	
Age in years	55.86 ± 4.94	60.82 ± 14.08	< 0.001
Nodule Size (cm)	2.52 ± 1.30	2.11 ± 1.01	< 0.001
TIRADS	3.35 ± 1.04	3.34 ± 1.06	0.458
Bethesda	2.21 ± 0.72	2.11 ± 0.75	0.091

SD = standard deviation, TIRADS = Thyroid Imaging Reporting and Data System

Figure 1. Distribution of patients by sex and nodule type

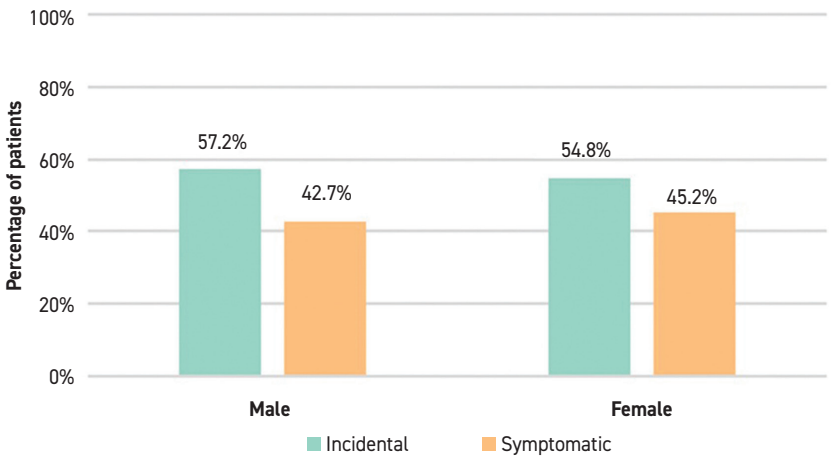

Table 2. Comparison between symptomatic and incidental patients according to sex, method of nodule detection, number of nodules, surgery, and pathology results

		Symptomatic patients		Incidental patients		*P*-value
		n	%	n	%	
Sex	Female	132	73.7%	160	71.7%	0.656
	Male	47	26.3%	63	28.3%	
Method of nodule detection	Computed tomography	2	1.1%	139	62.3%	< 0.001
	Ultrasound	174	97.2%	69	30.9%	
	Magnetic resonance imaging	2	1.1%	2	0.9%	
	^{18}F-FDG PET/CT	1	0.6%	12	5.4%	
	Radionuclide thyroid imaging	0	0.0%	1	0.4%	
Number of nodules	1	162	90.5%	206	92.4%	0.828
	2	16	8.9%	16	7.2%	
	3	1	0.6%	1	0.4%	
Surgery	No	165	92.1%	197	88.3%	0.214
	Yes	11	0.61%	24	10.7%	
	NA	3	0.16%	2	0.08%	
Pathology results	Benign	7	63.3%	18	75%	0.489
	Malignant	4	36.3%	6	25%	

^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography

nificant difference was found between symptomatic and incidental nodules (chi-square test, $P = 0.489$).

In addition, the study analyzed the population based on sex (male/female), examining variables such as the average age at nodule detection, nodule size, TIRADS score, and Bethesda classification score, as shown in Table 3.

Table 3 shows a significant difference in the average TIRADS score between females (3.28) and males (3.52), with $P < 0.05$. This shows that the suspicion of malignancy in thyroid nodules, both incidental and symptomatic, is higher in males than in females. However, no significant differences were observed between the sexes regarding age, nodule size, or Bethesda score ($P = 0.229$, $P = 0.078$, $P = 0.104$, respectively).

When the number of nodules was stratified by sex, a single nodule was the most common finding in both females and males (n=263, 90% and n=105, 95%).

Furthermore, Table 3 demonstrates statistically significant differences between benign and malignant nodules. Malignant nodules were detected at a younger age than benign nodules ($P < 0.05$), with their average size being smaller ($P < 0.05$) and a higher TIRADS score ($P < 0.01$). However, no statistically significant difference was observed in the Bethesda classification between malignant and benign nodules ($P = 0.055$).

DISCUSSION

In this study, we examined the clinical and demographic characteristics of 402 patients with thyroid nodules treated at our institution between 2018 and 2023. Sex distribution within the study population revealed a higher prevalence of thyroid nodules among females (72.6%). A review by Durante and colleagues [5] reported that thyroid nodules are more common in females. The average age of male and female patients was similar, suggesting that thyroid nodules affect a wide age range. These findings are generally consistent with literature, although slightly higher than in some reports. Moon et al. [6] reported a mean age of 49.5 years across 831 patients with thyroid nodules, approximately 10 years younger on average than our cohort. Classification by sex and mode of nodule detection showed that the proportion of incidental nodules was nearly identical between females and males: 55% and 57%, respectively. This proportion is contrary to findings by a large-scale study in China of over 13 million people in which the prevalence of thyroid nodules detected by ultrasonography was 44.7% in females and 29.9% in males. This finding could be related to sex differences in performing imaging studies or other reasons [7].

Table 3. Comparison of sex and pathological examination regarding age, nodule size, TIRADS, and Bethesda classification

	Female	Male	P-value	Benign (n=26)	Malignant (n=9)	P-value
Age in years, mean ± SD	58.30 ± 14.95	59.52 ± 13.89	0.229	56.50 ± 9.49	48.56 ± 14.59	0.035
Nodule size (cm), mean ± SD	2.24 ± 1.14	2.43 ± 1.23	0.078	2.87 ± 1.04	2.10 ± 0.65	0.024
TIRADS, mean ± SD	3.28 ± 1.05	3.52 ± 1.03	0.021	3.50 ± 0.86	4.33 ± 0.87	0.009
Bethesda, mean ± SD	2.12 ± 0.65	2.23 ± 0.92	0.104	3.15 ± 0.78	3.67 ± 0.87	0.055

SD = standard deviation, TIRADS = Thyroid Imaging Reporting and Data System

An in-depth analysis of age and nodule size showed significant differences between groups of patients with symptomatically detected nodules versus those found incidentally. Symptomatic patients were generally younger (mean age 55.9 years) and had larger nodules compared to patients with incidentally detected nodules. These findings indicate that larger nodules are more likely to cause symptoms and be detected earlier. In contrast, smaller nodules may remain asymptomatic and are more frequently identified incidentally at an older age. Jansen et al. [8] found that incidentalomas were smaller compared to clinically overt nodules. Specifically, 48.7% of incidentalomas were less than 2 cm in size, whereas only 23.4% of non-incidentalomas were less than 2 cm [8]. Interestingly, no significant differences were found in TIRADS or Bethesda scores, indicating that the risk of malignancy does not differ substantially between symptomatic and incidentally detected nodules. These observations underscore the importance of not dismissing incidental nodules, as their malignancy potential is comparable to symptomatic nodules. Further studies could investigate whether the size of a nodule correlates with the timing of its detection in older patients.

An analysis of the diagnostic methods for thyroid nodules revealed that ultrasound was the predominant imaging modality among symptomatic patients (97.2%), whereas incidental nodules were most often identified through computed tomography (CT) scans (62.3%). This pattern is consistent with current clinical approaches. Gharib et al. [9] noted that the American Association of Clinical Endocrinologists guidelines recommend ultrasound as the preferred initial imaging for symptomatic thyroid enlargement or suspected nodules. CT and magnetic resonance imaging frequently detect incidental thyroid nodules during evaluations for other conditions. This distinction likely reflects the different clinical pathways taken by the two groups. Symptomatic patients are often assessed with targeted ultrasound based on their presenting symptoms, while incidental nodules are usually discovered during CT scans conducted for unrelated reasons. These observations highlight the varying diagnostic approaches and emphasize the importance of customizing clinical strategies according to the method of detection.

Significantly, there were no differences in the rates of thyroid nodules malignancy found during thyroidectomy between symptomatic cases and incidental findings. This finding emphasizes the importance of thorough evaluation and thoughtful consideration of surgical management for all thyroid nodules, regardless of how they were detected. Future studies, which include larger sample sizes and focus on surgically excised nodules and their pathological outcomes, may provide deeper insight into potential distinctions between symptomatic and incidental nodules.

A comprehensive analysis of the study population by sex provides valuable insights into the distinct clinical characteristics of thyroid nodules in males and females. Examination of parameters such as age, nodule size, TIRADS, and Bethesda scores revealed notable differences. A significant disparity in mean TIRADS scores was observed between sexes, with females showing an average score of 3, indicating mild suspicion, and males showing an average score of 4, reflecting moderate suspicion. While sex can influence the risk of malignancy in thyroid nodules, the TIRADS score itself is determined by the ultrasound characteristics of the nodules rather than the patient's sex.[8] Therefore, the TIRADS score should be consistent regardless of sex, assuming the sonographic features are the same [10]. This higher prevalence of suspicious thyroid nodules in males, regardless of whether they were symptomatic or incidental, underscores the need for further investigation into potential sex-specific risk factors or mechanisms driving this phenomenon. The findings suggest that diagnostic and management strategies for thyroid nodules may benefit from tailored approaches based on sex-specific profiles.

Our cohort indicates that a single nodule was the most common presentation in terms of nodule count. This finding is supported by a systematic review and meta-analysis, which found that multiple incidentalomas were present in 27% of patients undergoing CT scans [11]. Our study

showed a notably higher prevalence of solitary nodules than average, which may reflect regional differences or referral patterns. The absence of significant sex-related differences in the number of nodules aligns with existing literature, supporting that thyroid nodule multiplicity is not inherently influenced by sex [12,13]. This consistency provides additional context for understanding the natural history of thyroid nodules while emphasizing the importance of addressing the observed variations in nodule suspicion rates between sexes.

The distribution of thyroid nodules based on pathology (benign or malignant) indicates significant differences between the groups. Malignant nodules were found to occur at a younger age, with a smaller average size and higher TIRADS scores compared to benign nodules. This finding aligns the established literature, which generally associates malignant nodules with younger age [14]. Several studies support this observation. For example, Walter and colleagues [15] found that the rate of malignant cytology in thyroid nodules decreases with increasing age, indicating that younger patients are more likely to have malignant nodules. In addition, Jansen and co-authors [8] reported that incidentalomas are generally smaller and less often symptomatic compared to non-incidentalomas, with a lower overall malignancy rate. Our finding that higher TIRADS scores correlate with malignancy confirms the utility of this classification system. Furthermore, the correlation between TIRADS scores and malignancy risk is well-documented. Atar et al. [16] demonstrated that higher TIRADS scores are associated with increased malignancy rates, with TI-RADS 5 nodules showing the highest risk. Altogether, these results suggest the presence of a unique subgroup within the overall population of patients with thyroid nodules: younger patients with smaller nodules that exhibit a TIRADS score indicating moderate suspicion for malignancy.

Our study highlights the importance of characterizing young patients within this subgroup, as their nodules may exhibit unique pathophysiology or clinical behavior. Incorporating such insights into the management and monitoring of thyroid nodules could improve diagnostic and treatment strategies, emphasizing the need to identify and address subgroups within the broader population of thyroid nodule patients.

Furthermore, although differences in Bethesda scores between malignant and benign nodules did not reach statistical significance ($P = 0.055$), the data suggest a potential trend in the pathological characteristics of these nodules. A larger study with an expanded sample size might achieve statistical significance, further elucidating these distinctions.

Our cohort represents a population in the Galilee region. The geographic maldistribution of healthcare resources in Israel, including the northern periphery, has been documented to impact health outcomes. Specifically, disparities in access to healthcare services, including specialist care, are more pronounced in peripheral regions compared to central areas [17]. This maldistribution may lead to delays in the diagnosis and treatment of conditions such as thyroid nodules. A study examining the accessibility of health services in Israel's southern periphery found that distance from healthcare facilities and socioeconomic status negatively correlated with the number of patient visits to specialist clinics [18]. This finding is likely applicable to the northern periphery as well, suggesting that residents in these areas may experience delays in accessing diagnostic and treatment services for thyroid nodules. Another study found that the overall 5-year survival of head and neck cancer for patients younger than 65 years of age and living in the center of the country was significantly higher than in the periphery [19]. In addition, the overall healthcare system in Israel, while advanced, still faces challenges in ensuring equal access across different regions. The Ministry of Health has recognized these disparities and has developed programs to address them, but significant gaps remain [17].

This study has several limitations. First, its retrospective nature may introduce selection bias, affecting the generalizability of the findings. Second, as the research was conducted at a single medical center, the results may be influenced by the center's specific patient population. A multi-center study could provide a more diverse cohort and yield different results. Furthermore, the study period coincided with the COVID-19 pandemic, which may have led to underreporting due to patients avoiding hospital visits [20]. Despite these limitations, the data were collected from a large medical center covering a broad geographical and cultural area over a wide time frame, which enhances the robustness of the findings.

CONCLUSIONS

We highlighted valuable insights into the demographic and clinical characteristics of patients with thyroid nodules. The prevalence of both incidental and symptomatic thyroid nodules was higher in females. Furthermore, the proportion of symptomatic nodules among all thyroid nodules was nearly identical in males and females. Although the study did not establish a higher malignancy rate in symptomatic nodules than incidental ones, we found that malignant nodules were more prevalent in younger patients with

smaller nodules. These variations underscore the complexity of thyroid nodules and emphasize the necessity for personalized diagnostic and management strategies, as there is an inverse relationship between patient age and nodule size with the risk of malignancy.

Acknowledgments

The article was written as part of the requirements of the Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel, for an MD degree. The authors thank Basem Hijazi from the Azrieli Faculty of Medicine for statistical analysis. This manuscript was edited for language and readability using a large language model. The content, data analysis, and interpretations are entirely the responsibility of the authors.

Correspondence

Dr. O. Ronen
Dept. of Otolaryngology–Head and Neck Surgery, Galilee Medical Center, Nahariya 2210001, Israel
Phone: (972-4) 910-7627
Fax: (972-4) 910-7671
Email: ohadr@gmc.gov.il

References

1. Chooi JE, Ravindiran A, Balasubramanian SP. The influence of incidental detection of thyroid nodule on thyroid cancer risk and prognosis-a systematic review. *Clin Endocrinol (Oxf)* 2022; 96 (2): 246-54.
2. Hoang JK, Langer JE, Middleton WD, et al. Managing incidental thyroid nodules detected on imaging: white paper of the ACR Incidental Thyroid Findings Committee. *J Am Coll Radiol* 2015; 12 (2): 143-50.
3. Russ G, Royer B, Bigorgne C, et al. Prospective evaluation of thyroid imaging reporting and data system on 4550 nodules with and without elastography. *Eur J Endocrinol* 2013; 168 (5): 649-55.
4. Cibas ES, Ali SZ; NCI Thyroid FNA State of the Science Conference. The Bethesda System for Reporting Thyroid Cytopathology. *Am J Clin Pathol* 2009; 132 (5): 658-65.
5. Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, Cooper DS. The diagnosis and management of thyroid nodules: a review. *JAMA* 2018; 319 (9): 914-924. Erratum in: *JAMA* 2018; 319 (15): 1622.
6. Moon WJ, Jung SL, Lee JH, et al; Thyroid Study Group, Korean Society of Neuro- and Head and Neck Radiology. Benign and malignant thyroid nodules: US differentiation--multicenter retrospective study. *Radiology* 2008; 247 (3): 762-70.
7. Li Y, Jin C, Li J, et al. Prevalence of thyroid nodules in China: a health examination cohort-based study. *Front Endocrinol (Lausanne)* 2021; 12: 676144.
8. Jansen T, Stikkelbroeck N, van de Ven A, et al. Clinical characteristics, diagnostic approach and outcome of thyroid incidental findings vs. clinically overt thyroid nodules: an observational single-centre study. *Cancers (Basel)* 2023; 15 (8): 2350.
9. Gharib H, Papini E, Garber JR, et al; AACE/ACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules-2016 Update. *Endocr Pract* 2016; 22 (5): 622-39.
10. Arena S, Benvenga S. The risk for malignancy of the thyroid nodule is modulated by gender, echotexture, and intranodular lymphocytic thyroiditis. *Horm Metab Res* 2019; 51 (9): 559-67.
11. Song Z, Wu C, Kasmirski J, et al. Incidental thyroid nodules on computed tomography: a systematic review and meta-analysis examining prevalence, follow-up, and risk of malignancy. *Thyroid* 2024; 34 (11): 1389-400.
12. Dean DS, Gharib H. Epidemiology of thyroid nodules. *Best Pract Res Clin Endocrinol Metab* 2008; 22 (6): 901-11.
13. Zou B, Sun L, Wang X, Chen Z. The prevalence of single and multiple thyroid nodules and its association with metabolic diseases in Chinese: a cross-sectional study. *Int J Endocrinol* 2020; 2020: 5381012.
14. Ospina NS, Papaleontiou M. Thyroid nodule evaluation and management in older adults: a review of practical considerations for clinical endocrinologists. *Endocr Pract* 2021; 27 (3): 261-8.
15. Walter LB, Fernandes PM, Strieder DL, et al. Age-related variation in malignant cytology rates of thyroid nodules: insights from a retrospective observational study assessing the ACR TI-RADS. *Eur J Endocrinol* 2023; 189 (6): 584-9.
16. Atar C, Dalcı K, Aktar Y, et al. Correlation of TIRADS scoring in thyroid nodules with preoperative fine needle aspiration biopsy and postoperative specimen pathology. *Head Neck* 2024; 46 (4): 849-56.
17. Clarfield AM, Manor O, Nun GB, et al. Health and health care in Israel: an introduction. *Lancet* 2017; 389 (10088): 2503-13.
18. Lubetzky H, Friger M, Warshawsky-Livne L, Shvarts S. Distance and socioeconomic status as a health service predictor on the periphery in the southern region of Israel. *Health Policy* 2011; 100 (2-3): 310-6.
19. Weizman B, Golan N, Ronen O. Effect of socioeconomic status on survival in patients with head and neck cancer. *Head Neck* 2021; 43 (10): 3001-9.
20. Medas F, Dobrinja C, Al-Suhaimi EA, et al; THYCOVID Collaboration Group. Effect of the COVID-19 pandemic on surgery for indeterminate thyroid nodules (THYCOVID): a retrospective, international, multicentre, cross-sectional study. *Lancet Diabetes Endocrinol* 2023; 11 (6): 402-13.

It has always seemed strange to me that in our endless discussions about education, so little stress is laid on the pleasure of becoming an educated person, the enormous interest it adds to life. To be able to be caught up into the world of thought–that is to be educated.

Edith Hamilton, (1868–1963), German educator and author

When I can look Life in the eyes, / Grown calm and very coldly wise, / Life will have given me the truth, / And taken in exchange--my youth.

Sara Teasdale (1884–1933), American lyric poet