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Polypharmacy and Potentially-Inappropriate Medications are Prevalent in the Elderly Cancer Patients Receiving Systemic Cancer Therapy and They Co-relate with Adverse Outcomes

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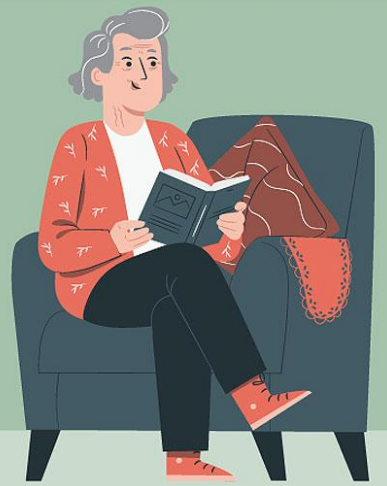
I have no relevant conflict of interest to be declared.

ASIA THE FASTEST AGEING SOCIETY IN THE WORLD

Thailand's ageing society is just behind Japan's "hyper-aged" society, followed by "aged" South Korea and "ageing" Singapore, and slightly ahead of Vietnam.



% of population aged 65+

	Japan	South Korea	Singapore	Thailand	Vietnam
2040	34%	31%	30%	26%	17%
2020	29%	16%	15%	13%	8%

Hyper-aged (20%) ← Aged (14%) ← Ageing (7%)

Ageing Process at present

Source: UN Population Prospect, 2015

BANGKOK POST GRAPHICS

INTRODUCTION

We are now approaching the ageing society.

- The more patient ages, the greater number of medications are prescribed. *(Azad , et al)*
- Among elderly cancer patients, both **polypharmacy (PP)** and **potentially-inappropriate medications (PIMs)** were associated with
  - Medical futility,
  - Increased risk of toxicities from cancer treatment, and treatment discontinuation *(Mohammed et al.),*
  - Unplanned hospitalizations *(Sganga et al.)* and
  - Death *(Jyrkkä et al.)*

- Azad N, Tierney M, Victor G, Kumar P. Adverse drug events in the elderly population admitted to a tertiary care hospital. J Healthc Manag. 2002;47(5):295–305.
- Mohamed MR, Ramsdale E, Loh KP, Arastu A, Xu H, Obrecht S, Castillo D, Sharma M, Holmes HM, Nightingale G, Juba KM, Mohile SG. Associations of polypharmacy and inappropriate medications with adverse outcomes in older adults with cancer: a systematic review and meta-analysis. Oncologist. 2020;25(1):e94–108.
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- Jyrkkä J, Enlund H, Korhonen MJ, Sulkava R, Hartikainen S. Polypharmacy status as an indicator of mortality in an elderly population. Drugs Aging. 2009;26(12):1039–48.

- **Polypharmacy (PP):** "The use of multiple medications and/or the administration of more medications than are clinically indicated and representing unnecessary drug use". *(Hajjar et al.)*
- 39% prevalence (as defined as regularly using ≥ 5 medications a day) overall in European countries *(Jörgensen, et al.)*
  - Most commonly-prescribed drugs including CVS, NS, and GI medications.
- 47.8% prevalence overall in Asian countries (11.9% had hyper-PP; ≥10 medications a day)) *(Cho et al.)*
  - Male sex, older age, co-morbidities (cardio-cerebrovascular disease, DM, depressive disorder, dementia, an Elikhauser co-morbidity index > 3), insurance and healthcare service utilization were associated with an increased probability of PP.

- Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. Am J Geriatr Pharmacother. 2007;5(4):345–51.
- Jörgensen T, Johansson S, Kennerfalk A, Wallander MA, Svärdsudd K. Prescription drug use, diagnoses, and healthcare utilization among the elderly. Ann Pharmacother. 2001;35(9):1004–9.
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- **Among elderly cancer patients,**
  - 35% PP prevalence (vs 27% of controls).
    - Analgesics, acid-suppressing drugs, and antibiotics were the most commonly-prescribed drugs. *(Jörgensen, et al.)*
  - 84% had PP and 43% had hyper-PP. *(Nightingale, et al.)*
  - 58% had PP. *(Yeoh, et al.)*
  - 23.1% in curative setting and 32.6% in the palliative setting had PP.
    - The increased number of medications was associated with the progression of cancer. *(Takemoto, et al.)*

- Jörgensen T, Johansson S, Kennerfalk A, Wallander MA, Svärdsudd K. Prescription drug use, diagnoses, and healthcare utilization among the elderly. Ann Pharmacother. 2001;35(9):1004–9.
- Nightingale G, Hajjar E, Swartz K, Andrel-Sendecki J, Chapman A. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inap- propriate medication use among ambulatory senior adults with cancer. J Clin Oncol. 2015;33(13):1453–9.
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- Right now, the cancer treatment has been more tailored based on molecular biomarkers; however, it is rarely customized based on a patient's physical functions.
- In the era of molecular-targeted therapy, the incidence/prevalence of PP and PIMs and their consequence to cancer outcomes have not yet particularly determined.
- We conducted an observational prospective cohort study to determine the prevalence of PP and PIMs among elderly cancer patients eligible for active cancer care and their associations with hospitalization and mortality.

METHODS

- **Inclusion criteria:**
  - Cancer patients aged ≥ 65 years old who had recently been diagnosed to have solid malignancies (excluding hematologic cancers).
  - Those whom a medical oncologist had decided to treat with systemic cancer treatments (cytotoxic agents or targeted therapies or both).
  - Every eligible participant was progressively followed up at least 1 year.
- **Exclusion criteria:**
  - Those who deserved only supportive or end of life care only due to any reasons (flail or unfitted conditions as a result of serious pre-existing condition(s), or patient and/or his caregivers' intents of no aggressive cancer management).
  - Those who had not attended regular visits during the first year after cancer diagnosis.

Definition of variables

- Besides demographic data were collected, the medication review included
  - ***medications prior to cancer diagnosis*** defined as any medications prescribed from 2 weeks - 1 year before cancer diagnosis and
  - ***medications after cancer diagnosis*** defined as any medications prescribed concomitant with active cancer treatment.
- The maximal numbers of such medications at any time in the last 1 year prior to cancer diagnosis and during active cancer care were recorded and used as whether participants had PP and PIMs.

- ***Polypharmacy (PP)*** *was defined as* ≥ 5 medications daily excluding anti-cancer drugs (cytotoxic agents and/or targeted therapies) and ***hyper-polypharmacy (hyper-PP)*** *was defined* as ≥10 medications daily excluding anti-cancer drugs.
- ***Corrected PP*** was defined as PP with exclusion of opioid analgesics, laxatives and anti-emetic agents, the most common concomitantly prescribed as the supportive care drugs for cancer patients.

- ***Potentially inappropriate medications (PIMs)*** was categorized using the 2019 Beers criteria, endorsed by the American Geriatrics Society.
- ***Unplanned hospitalization*** *was* defined as any hospitalizations due to any causes except from anti-cancer treatment administration or in-patient clinical investigations such as imaging studies and endoscopic examinations scheduled to be obtained unrelated to a patient's worsening clinical condition.
- ***Charlson co-morbidity index (CCI)*** was used to evaluate the degree of seriousness of pre-existing medical conditions.
- ***1-year survival rate*** *was* defined as the proportion of patients who survived 1-year after cancer diagnosis.

- **Primary outcome:** Prevalence of PP in cancer patients suitable for systemic cancer therapy.
- **Secondary outcomes:**
  - Prevalence of hyper-PP,
  - Associations between PP and other baseline demographics,
  - Rate of unexpected hospitalization and
  - 1-year survival.
  - Prevalence of PIMs.

OUTCOMES

- Enrollment of participants occurred between January 1, 2021 to December 31, 2022.
- There were 236 elderly patients with non-hematologic cancer aged more than 65 years old, 198 of them were eligible for systemic cancer treatment and 18 of them were later excluded due to loss to follow up during a year after cancer diagnosis.
- At least of 1 year of follow-up was required to determine survival rate.

Baseline characteristics of participants

- 67.78% had PP.
- 20% had hyper-PP

	Total *n* = 180	non-Polypharmacy (< 5) *n* = 58	Polypharmacy (> 5) *n* = 122
Age (years) (Median (IQR))	68 (65–73)	68 (65–71)	68.5 (65–74)
Male:Female (N (%))	100 (55.56): 80 (44.44)	27 (46.6): 31 (53.4)	73 (59.8): 49 (40.2)
Type of Cancer (N (%))			
CA lung	31	7 (12.1%)	24 (19.7%)
CA breast	35	19 (32.8%)	16 (13.1%)
CA colon	18	7 (12.1%)	11 (9%)
CA rectum	10	5 (8.6%)	5 (4.1%)
HCC	11	3 (5.2%)	8 (6.6%)
CA stomach	2	1 (1.7%)	1 (0.8%)
CA pancrease	6	2 (3.4%)	4 (3.3%)
CA bladder	16	2 (3.4%)	14 (11.5%)
CA prostate	7	0 (0%)	7 (5.7%)
CA esophagus	8	2 (3.4%)	6 (4.9%)
CA head and neck	17	4 (6.9%)	13 (10.7%)
Sarcoma	4	4 (6.9%)	0 (0%)
Melanoma	1	1 (1.7%)	0 (0%)
Cholangiocarcinoma	4	1 (1.7%)	3 (2.5%)
Other	10	0 (0%)	10 (8.2%)
Stage (N (%))			
Stage 1–3	94	34 (58.6%)	60 (49.2%)
Stage 4	86	24 (41.4%)	62 (50.8%)
Charlson Co-morbidity Index (Median (IQR))	8 (5–9)	5 (4–8)	8 (5–9)
Number of Medications (Median (IQR))			
Prior to cancer diagnosis	3 (0–6.5)	1 (0–2)	4.5 (2–8)
After cancer diagnosis	6 (4–8)	3 (2–4)	7 (6–10)

List of medications used among patients with PP

Medications	n (%)
Drugs used in cardiovascular diseases	87 (71.3%)
Anti-hypertensive	66 (54.1%)
Anti-platelet	18 (14.8%)
Anti-coagulant	3 (2.5%)
Opioids	73 (60.3%)
Laxatives	72 (59%)
Proton pump inhibitors (PPI)	65 (53.3%)
Antibiotics	65 (53.3%)
Anti-emetics	60 (49.2%)
Sedatives	45 (36.9%)
Anti-hyperlipidemic agents	37 (30.3%)
Gabapentin	33 (27%)
Anti-diabetic	29 (23.8%)
NSIADs	23 (18.9%)
Psychoactive agents	7 (5.7%)
Steroids	7 (5.7%)
Hormonal agents	6 (4.9%)
Antacids	4 (3.3%)

List of medications used among patients with PIMs

- 69.4% had PIMs.

Medications	n (%)
First-generation anti-histamine	6 (2.67%)
Anti-parkinsonian agents	1 (0.44%)
Anti-spasmodics	8 (3.56%)
Peripheral alpha-1 blockers	22 (9.78%)
Digoxin	2 (0.89%)
Anti-depressants	7 (3.11%)
Anti-psychotic	14 6.22%)
Benzodiazepines	46 (20.44%)
Non-benzodiazepine anxiolytics	2 (0.89%)
Desiccated thyroid extract	3 (1.33%)
Insulins	1 (0.44%)
Metoclopramide	6 (2.67%)
Proton pump inhibitors (PPIs)	72 (32%)
COX-2 inhibitors and non-selective NSIADs	14 (6.22%)
Skeletal muscle relaxant	21 (9.33%)

Associated factors determining the tendency of PP

	Non-Polypharmacy(< 5) $n = 58$	Polypharmacy (≥ 5) $n = 122$	Adjusted Odds ratio[a]	95%CI	*P*-value
Age					
< 70	43 (35.8%)	77 (64.2%)	1		
> = 70	15 (25%)	45 (75%)	1.13	0.52–2.48	0.759
Gender					
Male	27 (27%)	73 (73%)	1.56	0.81–3.01	0.188
Female	31 (38.8%)	49 (61.3%)	1		
Type of cancer					
Non-pulmonary cancer	51 (34.2%)	98 (65.8%)	1		
Primary pulmonary cancer	7 (22.6%)	24 (77.4%)	1.75	0.69–4.46	0.240
Stage					
Stage 1–3	34 (36.2%)	60 (63.8%)	1		
Stage 4	24 (27.9%)	62 (72.1%)	0.91	0.42–1.95	0.801
CCI					
< 5	20 (54.1%)	17 (45.9%)	1		
> = 5	38 (26.6%)	105 (73.4%)	3.09	1.19–8.01	0.021

[a] Logistic regression

Associated factors determining the tendency of PP[a]

	non-Polypharmacy (< 5)[a]	Polypharmacy (> 5)[a]	Adjusted	95%CI	*P*-value
	n = 106	*n* = 74	Odds ratio[b]		
Age					
< 70	76 (63.3%)	44 (36.7%)	1		
> = 70	30 (50%)	30 (50%)	1.20	0.60–2.40	0.606
Gender					
Male	56 (56%)	44 (44%)	1.16	0.62–2.18	0.644
Female	50 (62.5%)	30 (37.5%)	1		
Type of cancer					
Non-pulmonary cancer	90 (60.4%)	59 (39.6%)	1		
Primary pulmonary cancer	16 (51.6%)	15 (48.4%)	1.50	0.66–3.38	0.331
Stage					
Stage 1–3	56 (59.6%)	38 (40.4%)	1		
Stage 4	50 (58.1%)	36 (41.9%)	0.64	0.32–1.26	0.192
CCI					
< 5	30 (81.1%)	7 (18.9%)	1		
> = 5	76 (53.1%)	67 (46.9%)	4.41	1.57–12.34	0.005

[a] Excluding opioid analgesics, laxatives, and anti-emetics

[b] Logistic regression

Association between PIMs and baseline characteristics

	No PIM $n=55$	PIMs $n=125$	Adjusted Odds ratio[a]	95%CI	*P*-value
Age					
<70	39 (32.5%)	81 (67.5%)	1		
>=70	16 (26.7%)	44(73.3%)	0.87	0.40–1.92	0.735
Gender					
Male	29 (30.9%)	65 (69.1%)	1.06	0.55–2.07	0.857
Female	26 (30.2%)	60(69.8%)	1		
Type of cancer					
Non-primary lung cancer	18 (48.6%)	19 (51.4%)	1		
Primary pulmonary cancer	37 (25.9%)	106 (74.1%)	1.29	1.52–3.19	0.006
Stage					
Stage 1–3	47 (31.5%)	102 (68.5%)	1		
Stage 4	8 (25.8%)	23 (74.2%)	0.57	0.26–1.26	0.163
CCI					
<5	29 (29%)	71 (71%)	1		
>=5	26 (32.5%)	54 (67.5%)	3.96	0.48–10.65	0.583

[a] Logistic regression

Associated Factors of 1-year Mortality

	Survived		Died		Un-adjusted	95%CI	*P*-value	Adjusted	95%CI	*P*-value
	n	%	n	%	OR			OR[a]		
Age										
< 70	98	81.7	22	18.3	1			1		
> = 70	41	68.3	19	31.7	1.82	0.99–3.37	0.06	2.24	1.14–4.41	0.019
Gender										
Male	73	73	27	27	1.61	0.85–3.08	0.15	1.25	0.65–2.44	0.504
Female	66	82.5	14	17.5	1			1		
Type of cancer										
Non-primary lung cancer	121	81.2	28	18.8	1			1		
Primary lung cancer	18	58.1	13	41.9	2.58	1.34–4.99	0.005*	2.89	1.45–5.78	0.003
Stage										
Stage 1–3	86	91.5	8	8.5	1			1		
Stage 4	53	61.6	33	38.4	5.45	2.51–11.80	< 0.001*	4.57	1.90–10.97	0.001
CCI										
< 5	35	94.6	2	5.4	1			1		
> = 5	104	72.7	39	27.3	5.70	1.38–23.60	0.016*	1.19	0.23–6.17	0.840
Polypharmacy*										
< 5	85	80.2	21	19.8	1			1		
> = 5	54	73	20	27	1.41	0.76–2.60	0.27	0.95	0.49–1.83	0.875
Unplanned hospitalizations										
No	117	84.8	21	15.2	1			1		
Yes	22	52.4	20	47.6	3.84	2.08–7.10	< 0.001*	3.09	1.60–5.99	0.001

* Excluding opioid analgesics, laxatives and anti-emetics

[a] Cox's Proportional Hazard Model

Factors Associated with Unplanned Hospitalizations

	No unplanned hospitalization		Unplanned hospit hospitalization		Unadjusted	95%C.I	*P*-value	Adjusted	95%C.I	*P*-value
	n	%	n	%	OR			OR[a]		
Age										
<70	94	78.3	26	21.7	1			1		
>=70	44	73.3	16	26.7	1.39	0.74–2.59	0.30	1.27	0.64–2.53	0.488
Gender										
Male	69	69	31	31	2.45	1.23–4.88	0.01*	2.35	1.17–4.71	0.016
Female	69	86.3	11	13.8	1			1		
Type of cancer										
Non-primary lung cancer	115	77.2	34	22.8	1			1		
Primary lung cancer	23	74.2	8	25.8	1.43	0.66–3.10	0.36	1.40	0.63–3.12	0.412
Stage										
Stage 1–3	79	84	15	16	1			1		
Stage 4	59	68.6	27	31.4	2.65	1.41–4.98	0.003*	2.74	1.33–5.66	0.006
CCI										
<5	32	86.5	5	13.5	1			1		
>=5	106	74.1	37	25.9	2.33	0.92–5.93	0.08	0.87	0.28–2.71	0.803
Corrected polypharmacy *										
<5	88	83.0	18	17.0	1			1		
>=5	50	67.6	24	32.4	2.03	1.10–3.74	0.02*	1.90	1.012–3.557	0.046

* Excluding opioid analgesics, laxatives, and anti-emetics

[a] Cox's Proportional Hazard Model

CONCLUSIONS

- 67.78% of participants had PP and 20% had hyper-PP.
- Among elderly cancer patients with **extreme age**, **primary lung cancer**, **metastatic disease at cancer diagnosis** were the most vulnerable subgroups that an oncologist should determine a specific cancer management meticulously.

- Even though PP and PIMs did not directly result in mortality per se, they were associated with **unplanned hospitalizations**.
  - Increased medical costs
  - Disturbed quality of life
  - Patient's life trajectory

DISCUSSION

- The most recent data from the Western countries by *Ramsdale, et al.* reported 61.3% of the elderly cancer patients had PP (≥5 medications) and 14.5% of them had hyper-PP (≥ 10 medications).

- Ramsdale E, Mohamed M, Yu V, Otto E, Juba K, Awad H, Moorthi K, Plumb S, Patil A, Vogelzang N, Dib E, Mohile S. Polypharmacy, potentially inap- propriate medications, and drug-drug interactions in vulnerable older adults with advanced cancer initiating cancer treatment. Oncologist. 2022;27(7):e580–8.

- *Turner, et al.* evaluated the prevalence and factors associated with PP in the elderly cancer patients and demonstrated that when adjusting for age, sex, IADLs, Karnofsky Performance Scale (KPS), physical function (using SF-36), pain (using 10-point VAS), exhaustion (using CES-D) and distress (using 10-point VAS), ***higher CCI was remained the independent predictor of PP***.

- Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, Johns S, Bell JS. Prevalence and factors associated with polypharmacy in older people with cancer. Support Care Cancer. 2014;22(7):1727–34.

- As a result of the difficulty in determining serious ***potentially clinically significant drug-drug interactions (PDIs),*** we evaluated the association between PP/PIMs and unplanned hospitalizations instead.

- Both corrected PP (excluding opioids, laxatives and anti-emetics) and hyper-PP, male gender and metastatic disease at cancer diagnosis were the independent factors associated with unplanned hospitalizations.
  - Due to non-specific presentations among the elderly patients, we proposed that altered consciousness presumptively diagnosed to have sepsis and metabolic disturbances would rather be the manifestations of undesired side effects from drug interactions from excessive medications used.

- Due to the ever-changing numbers of prescribed medications and their exact duration of truly-administered drugs, we found inconclusive effect of PIMs to survival and hospitalizations.
- Based on historical data, there were inconclusive evidences demonstrating the detrimental effects of PP and PIMs among cancer patients.
- A systemic review and meta-analysis by *Mohamed et al.* concluded that even though various definitions of PP, heterogeneities in terms of both study designs and populations, PP was associated with post-operative complications, chemotherapy toxicities and both physical and functional decline.

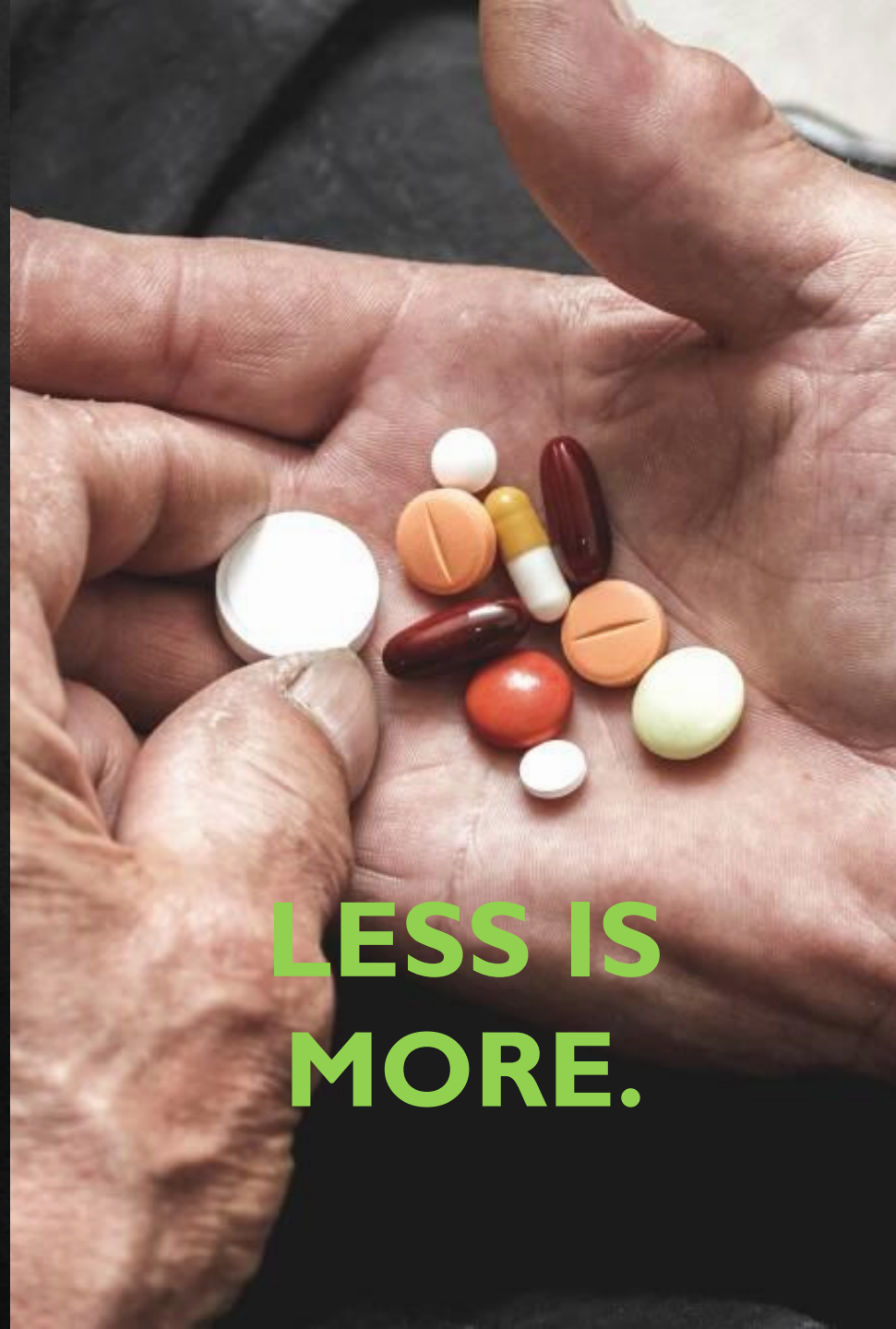
- Mohamed MR, Mohile SG, Juba KM, Awad H, Wells M, Loh KP, Flannery M, Culakova E, Tylock RG, Ramsdale EE. Association of polypharmacy and potential drug-drug interactions with adverse treatment outcomes in older adults with advanced cancer. Cancer. 2023;129(7):1096–104.

- Even though cancer is the disease of ageing; however, age alone should not be the solitary factor of exclusion of ageing patients from active cancer treatment.
- Co-morbidities and ageing exist independently and the prevalence of co-morbid conditions climbs with increasing age.
- The comprehensive geriatric assessment (CGA) can provide extensive information of both functional and physiological age of an elderly person with cancer in particular.
  - Several domains, including physical function, cognition, nutrition, comorbidities, psychological status, and social support are evaluated together.
- The multi-comorbidity was not the independent factor for survival in this elderly cancer patients' cohort; however, ***a probability of the fact that some co-morbid conditions were more predictive than the others cannot be excluded.***

SUGGESTIONS

- Among elderly cancer patients, the number of prescribed drugs depended on a pre-existing patient's co-morbidity; therefore, it would be possible to prescribe as least as possible, only if physicians judiciously determined the necessity.
- Extreme ageing cancer patients and primary lung cancer, metastatic disease at diagnosis were associated with shorter survival.
  - Such vulnerable patients were among those who needed comprehensive geriatric assessment (CGA) to determine the most proper cancer care.

- Cancer patients with extreme age, metastatic disease at diagnosis and PP had strong tendency towards more unplanned hospitalizations.
- A physician should be more vigilant in taking care and prescribing such patients who are more likely to succumb to serious adverse events.



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